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ORIGINAL REPORT

Nivolumab in Combination With Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose

Nivolumab, a fully human immunoglobulin G4 programmed death-1 immune checkpoint inhibitor antibody, has demonstrated improved survival in previously treated patients with advanced non–small-cell lung cancer (NSCLC). CheckMate 012, a phase I, multicohort study, was conducted to explore the safety and efficacy of nivolumab as monotherapy or combined with current standard therapies in first-line advanced NSCLC. Here, we report results for nivolumab plus platinum-based doublet chemotherapy (PT-DC).

Patients and Methods

Patients (N = 56) received nivolumab (intravenously) plus PT-DC concurrently every 3 weeks for four cycles followed by nivolumab alone until progression or unacceptable toxicity. Regimens were nivolumab 10 mg/kg plus gemcitabine-cisplatin (squamous) or pemetrexed-cisplatin (nonsquamous) or nivolumab 5 or 10 mg/kg plus paclitaxel-carboplatin (all histologies). The primary objective was to assess safety and tolerability. Secondary objectives included objective response rate and 24-week progression-free survival rate (per Response Evaluation Criteria in Solid Tumors version 1.1); exploratory objectives included overall survival (OS) and response by tumor programmed death ligand-1 expression.

Results

No dose-limiting toxicities occurred during the first 6 weeks of treatment. Forty-five percent of patients (25 of 56 patients) reported grade 3 or 4 treatment-related adverse events (AEs); 7% of patients (n = 4) had pneumonitis. Twenty-one percent of patients (n = 12) discontinued all study therapy as a result of treatment-related AEs. Objective response rates for nivolumab 10 mg/kg plus gemcitabine-cisplatin, nivolumab 10 mg/kg plus pemetrexed-cisplatin, nivolumab 10 mg/kg plus paclitaxel-carboplatin, and nivolumab 5 mg/kg plus paclitaxel-carboplatin were 33%, 47%, 47%, and 43%, respectively; 24-week progression-free survival rates were 51%, 71%, 38%, and 51%, respectively; 2-year OS rates were 25%, 33%, 27%, and 62%, respectively. Responses were achieved regardless of tumor programmed death ligand-1 expression.

Conclusion

The safety profile of nivolumab plus PT-DC was consistent with that expected for individual agents; however, treatment discontinuation related to AEs was greater with the combination. Encouraging activity was observed, especially for the nivolumab 5 mg/kg plus paclitaxel-carboplatin group, with a 2-year OS rate of 62%.

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INTRODUCTION

Platinum-based doublet chemotherapy (PT-DC) is the standard of care as first-line therapy for patients with non–oncogenic-driven advanced (stage IIIb/IV) non–small-cell lung cancer (NSCLC).[1] Randomized studies comparing various PT-DC regimens have yielded similar efficacy results, demonstrating objective response rates (ORRs) of 15% to 32%; median progression-free survival (PFS) and overall survival (OS) times of 4.0 to 5.1 and 8.1 to 10.3 months, respectively; and 1- and 2-year OS rates of 30% to 44% and 10% to 18.9%,

respectively.[1-6] Bevacizumab and maintenance chemotherapy, most commonly with pemetrexed, have improved clinical outcomes (median PFS: maintenance bevacizumab, 3.7 to 6.9 months; maintenance pemetrexed, 7.5 months; maintenance bevacizumab plus pemetrexed, 7.4 to 8.6 months).[7-9] However, resistance to chemotherapeutic agents invariably develops, and all patients eventually experience progression.[10]

Although conventional chemotherapy directly targets tumor cell replication strategies, preclinical evidence demonstrates that chemotherapeutic agents are less effective in immunodeficient hosts, suggesting the antitumor effects of cytotoxic chemotherapy also occur through modulation of the immune system.[11,12] Consistent with this idea, anthracycline and platinum agents engage signaling pathways that lead to immunogenic cell death, triggering the uptake and processing of tumor antigens.[12-14] Furthermore, gemcitabine inhibits B-cell proliferation and selectively depletes immunosuppressive myeloid-derived suppressor cells and regulatory T cells in mouse models of malignant mesothelioma and lung cancer.[15,16]

The immunogenic properties of conventional chemotherapy and rapid emergence of chemotherapy resistance provide a good rationale for combining PT-DC with immunotherapy, particularly immune checkpoint inhibitors.[10,13,14] Nivolumab, a fully human immunoglobulin G4 programmed death-1 (PD-1) immune checkpoint inhibitor antibody, binds with high affinity to PD-1 receptors on T cells, blocking their interaction with PD ligands 1 and 2 (PD-L1/PD-L2) and restoring T-cell antitumor function.[17,18] In two phase III randomized trials, nivolumab demonstrated superior OS versus docetaxel in patients with advanced squamous or nonsquamous NSCLC.[19,20] These results led to the approval of nivolumab in the United States for treatment of patients with metastatic NSCLC after platinum-based chemotherapy and tyrosine kinase inhibitor therapy if expressing epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase genomic tumor aberrations.[21] Nivolumab also is approved in the European Union for locally advanced or metastatic NSCLC after prior chemotherapy.[22]

Given the demonstrated safety and efficacy of nivolumab as second-line or later monotherapy, CheckMate 012 (ClinicalTrials.gov identifier: NCT01454102), a phase I, multicohort study, was designed to evaluate the potential benefit of nivolumab as monotherapy or combined with current standard therapies in first-line advanced NSCLC. Nivolumab monotherapy in this setting demonstrated an ORR of 23% and a 1-year OS rate of 74%.[23] Here, we report the safety and efficacy results of nivolumab plus three standard PT-DC regimens from four cohorts of this trial. Exploratory analyses of clinical activity by tumor PD-L1 expression, smoking history, and *EGFR* and Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutation status are also reported.

PATIENTS AND METHODS

Study Design

This study was approved by local institutional review boards, and all patients or their legal representatives provided written informed consent before enrollment. Patients with stage IIIB or IV NSCLC were assigned by histology to receive nivolumab 10 mg/kg plus gemcitabine-cisplatin (squamous) or pemetrexed-cisplatin (nonsquamous) or nivolumab 5 or 10 mg/kg plus paclitaxel-carboplatin (all histologies; Data Supplement). Nivolumab and PT-DC were administered intravenously on day 1 of each 21-day cycle (patients receiving gemcitabine-cisplatin also received chemotherapy on day 8) for four cycles followed by nivolumab monotherapy every 3 weeks at the same dose. Treatment was continued until progressive disease (PD), as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[24]; discontinuation as a result of toxicity; or withdrawal of consent. Patients who discontinued chemotherapy as a result of toxicity remained on the study and received nivolumab as monotherapy. Patients who discontinued nivolumab as a result of toxicity were withdrawn from the treatment phase of the study. Patients were permitted to continue nivolumab after initial progression if they were considered by the investigator to be deriving clinical benefit (continuing symptom or disease control despite radiographic progression) and tolerating study treatment.

The study used a dose de-escalation design on the basis of the modified toxicity probability interval method,[25] guided by the number of dose-limiting toxicities (DLTs) observed during the first two cycles (6 weeks) of therapy (Data Supplement). Whereas the nivolumab 10 mg/kg dose was based on results from an earlier trial,[26] the 5 mg/kg dose was added after a protocol amendment to assess the safety of a lower nivolumab dose in combination with paclitaxel-carboplatin (which can be used for all histologic subtypes). Addition of this arm was not driven by safety, because no DLTs were observed with nivolumab 10 mg/kg, but rather, it was added on the basis of pharmacokinetic modeling showing that nivolumab 5 mg/kg every 3 weeks provides a steady-state trough concentration equivalent to nivolumab 3 mg/kg every 2 weeks, the approved monotherapy dosing regimen.[17]

Follow-up visits after discontinuation of study therapy occurred 30 (± 14) and 100 (± 14) days from the last dose of study therapy. For patients who discontinued treatment for reasons other than PD, tumor assessments were performed every 3 months (± 14 days) until documented progression. Survival was evaluated every 12 weeks after the second visit. Patients were observed for treatment-related toxicities until they resolved, returned to baseline, or were deemed irreversible.

Participants

Eligible patients had newly diagnosed and histologically or cytologically confirmed stage IIIB or IV NSCLC,[27] with radiographic proof of measurable disease per RECIST v1.1. Patients were age 18 years or older with an Eastern Cooperative Oncology Group performance status of 0 or 1, adequate hematologic, hepatic, and renal function; and life expectancy ≥ 3 months. Patients had not received prior chemotherapy for advanced NSCLC; however, prior radiotherapy and *EGFR* tyrosine kinase inhibitor therapy were permitted if completed ≥ 2 weeks before study drug administration. Pretreatment tumor samples were collected for biomarker evaluation but were not used to select patients. Additional details regarding patient eligibility criteria are provided in the Data Supplement.

Concomitant Treatments

A brief course of corticosteroids was permitted for prophylaxis (eg, contrast dye allergy) or treatment of nonautoimmune conditions. Additionally, corticosteroid premedication for chemotherapy regimens and regimens for delayed nausea were permitted. Prohibited treatments are provided in the Data Supplement.

Study Assessments

Safety assessments. The primary objectives of safety and tolerability were measured by the frequency of treatment-related (PT-DC and/or nivolumab) adverse events (AEs) and through monitoring of laboratory abnormalities. Categories of select AEs (those with potential immunologic

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etiology that require more frequent monitoring or intervention) were based on a prespecified list from the Medical Dictionary for Regulatory Activities, version 17.0. The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[28]

Efficacy assessments. The secondary objective was antitumor activity of nivolumab plus PT-DC, as measured by ORR and PFS rate at 24 weeks using investigator-assessed tumor assessments according to RECIST v1.1.[24] Per the original study protocol, tumor response was first assessed at week 6. However, because early pseudoprogression may be observed at this time point, the protocol was amended to perform the first tumor assessment at week 10. Subsequent scans were performed at weeks 16 and 22 and then every 3 months thereafter until disease progression. For patients continuing nivolumab treatment beyond initial progression, tumor assessments continued until treatment discontinuation. OS was an exploratory efficacy end point. Clinical activity also was assessed by histology, smoking history, *EGFR* and *KRAS* mutation status, and tumor PD-L1 expression (Data Supplement).

Statistical Analyses

Sample size was based on 12 patients per arm, providing 90% probability of observing at least one occurrence of any AE that would occur with a 17% incidence. Analyses are based on a September 2014 database lock, with data for OS by treatment arm, histology, and mutation status updated as of March 2015. Patient demographics and frequency of AEs were summarized by arm using descriptive statistics. ORR was defined as the proportion of all treated patients whose best overall response (BOR) was either a confirmed complete or partial response, with two-sided 95% exact CIs calculated using the Clopper-Pearson method.[29] Estimated time to event end points (24-week PFS rate, median duration of response [DOR], PFS, and OS) were calculated using the Kaplan-Meier method, with two-sided 95% exact CIs derived via log-log transformation.[30]

RESULTS

Patient Characteristics

Fifty-six patients with advanced NSCLC were treated with nivolumab 10 mg/kg plus gemcitabine-cisplatin (n = 12), nivolumab 10 mg/kg plus pemetrexed-cisplatin (n = 15), nivolumab 10 mg/kg plus paclitaxel-carboplatin (n = 15), or nivolumab 5 mg/kg plus paclitaxel-carboplatin (n = 14). At baseline, 96% of patients (n = 54) had stage IV disease, 14% (n = 8) were never smokers, 11% (n = 6) had *EGFR*-mutant tumors, 18% (n = 10)

Table 1. Patient Baseline Characteristics

	No. of Patients (%)				
	Nivolumab 10 mg/kg			Nivolumab 5 mg/kg	
Characteristic	Gem-Cis (n = 12)	Pem-Cis (n = 15)	Pac-Carb (n = 15)	Plus Pac-Carb (n = 14)	All Patients (N = 56)
Age, years					
Median	67	60	58	64	64
Range	49-76	34-78	34-69	47–83	34-83
Sex					
Male	7 (58)	6 (40)	7 (47)	6 (43)	26 (46)
Female	5 (42)	9 (60)	8 (53)	8 (57)	30 (54)
Disease stage					
IIIB	1 (8)	0	0	1 (7)	2 (4)
IV	11 (92)	15 (100)	15 (100)	13 (93)	54 (96)
Histology					
Adenocarcinoma	0	15 (100)	10 (67)	12 (86)	37 (66)
Squamous cell carcinoma	12 (100)	0	3 (20)	1 (7)	16 (29)
Other	0	0	2 (13)	1 (7)	3 (5)
EGFR mutation status					
Mutant	0	4 (27)	1 (7)	1 (7)	6 (11)
Wild type	3 (25)	10 (67)	10 (67)	12 (86)	35 (63)
Unknown	9 (75)	1 (7)	4 (27)	1 (7)	15 (27)
KRAS mutation status					
Mutant	0	2 (13)	2 (13)	6 (43)	10 (18)
Wild type	4 (33)	7 (47)	4 (27)	4 (29)	19 (34)
Unknown	8 (67)	6 (40)	9 (60)	4 (29)	27 (48)
Smoking status					
Current	2 (17)	2 (13)	3 (20)	0	7 (13)
Former	10 (83)	10 (67)	9 (60)	11 (79)	40 (71)
Never	0	3 (20)	2 (13)	3 (21)	8 (14)
Unknown	0	0	1 (7)	0	1 (2)
Prior surgery	9 (75)	11 (73)	11 (73)	14 (100)	45 (80)
Prior radiotherapy	2 (17)	6 (40)	8 (53)	5 (36)	21 (38)
Prior treatment with erlotinib	0	2 (13)	1 (7)	0	3 (5)
Prior systemic therapy	2 (17)	2 (13)	2 (13)	2 (13)	4 (29)
Regimen setting*					
Adjuvant therapy	2 (17)	0	0	1 (7)	3 (5)
Metastatic disease	0	2 (13)	1 (7)	0	3 (5)
Neoadjuvant therapy	0	0	1 (7)	3 (21)	4 (7)

Abbreviations: Carb, carboplatin; Cis, cisplatin; Gem, gemcitabine; Pac, paclitaxel; Pem, pemetrexed.
*More than one setting per patient may be reflected in the frequency. Patients may have received prior chemotherapy as adjuvant or neoadjuvant therapy, but not for metastatic disease. All patients who received prior systemic therapy for metastatic disease were treated with erlotinib.

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had *KRAS*-mutant tumors, and 5% (n = 3) had received prior erlotinib (Table 1). Median follow-up time for safety and efficacy (ORR, PFS, and OS by PD-L1 expression) was 19.0 months (range, 3.2 to 29.7 months) across all patients and varied from 11.6 to 22.2 months across treatment arms. Median follow-up time for OS was 19.0 months (range, 3.2 to 35.1 months) across all patients and varied from 11.6 to 26.4 months across arms. At the time of analysis, 95% of patients (n = 53) had discontinued study treatment, most commonly as a result of disease progression (70%, n = 39; Data Supplement).

Safety

No DLTs were observed during the first 6 weeks of treatment with nivolumab 10 mg/kg plus PT-DC. In patients treated with nivolumab 10 mg/kg plus PT-DC, treatment-related AEs of any grade occurred in 93% of patients (39 of 42 patients), and grade 3 or 4 AEs occurred in 50% of patients (21 of 42 patients). In the overall population, 95% of patients (53 of 56 patients) and 45% of patients (25 of 56 patients) experienced any grade and grade 3 or 4 treatment-related AEs, respectively (Table 2). The most commonly reported (≥ 30% of patients) treatment-related AEs

Table 2. Treatment-Related AEs Reported in ≥ 10% of Patients in Any Arm With Advanced NSCLC Treated With Nivolumab Plus PT-DC

	No. of Patients (%)									
	Nivolumab 10 mg/kg						Nivolumab 5 mg/kg Plus Pac-Carb (n = 14)		All Patients (N = 56)	
	Gem-Cis (n = 12)		Pem-Cis (n = 15)		Pac-Carb (n = 15)					
Event	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any event	10 (83)	3 (25)	14 (93)	7 (47)	15 (100)	11 (73)	14 (100)	4 (29)	53 (95)	25 (45)
Fatigue	8 (67)	0	12 (80)	1 (7)	10 (67)	2 (13)	10 (71)	0	40 (71)	3 (5)
Nausea	8 (67)	0	10 (67)	1 (7)	2 (13)	0	6 (43)	0	26 (46)	1 (2)
Decreased appetite	6 (50)	0	7 (47)	0	5 (33)	1 (7)	2 (14)	0	20 (36)	1 (2)
Alopecia	2 (17)	0	1 (7)	0	10 (67)	0	4 (29)	0	17 (30)	0
Anemia	6 (50)	1 (8)	2 (13)	0	5 (33)	1 (7)	2 (14)	0	15 (27)	2 (4)
Rash	1 (8)	0	5 (33)	0	4 (27)	0	5 (36)	1 (7)	15 (27)	1 (2)
Diarrhea	2 (17)	0	2 (13)	0	5 (33)	1 (7)	3 (21)	0	12 (21)	1 (2)
Arthralgia	0	0	3 (20)	0	7 (47)	0	2 (14)	0	12 (21)	0
Constipation	1 (8)	0	4 (27)	0	3 (20)	0	3 (21)	0	11 (20)	0
Peripheral neuropathy	1 (8)	0	2 (13)	0	1 (7)	0	7 (50)	0	11 (20)	0
Dysgeusia	2 (17)	0	2 (13)	0	2 (13)	0	2 (14)	0	8 (14)	0
Hypersensitivity	1 (8)	0	3 (20)	1 (7)	4 (27)	0	0	0	8 (14)	1 (2)
Vomiting	2 (17)	0	4 (27)	0	0	0	2 (14)	0	8 (14)	0
Mucosal inflammation	2 (17)	0	1 (7)	0	1 (7)	0	3 (21)	0	7 (13)	0
Myalgia	0	0	0	0	2 (13)	0	5 (36)	0	7 (13)	0
Pneumonitis	2 (17)	1 (8)	3 (20)	2 (13)	0	0	2 (14)	1 (7)	7 (13)	4 (7)
Infusion-related reaction	0	0	4 (27)	0	2 (13)	0	0	0	6 (11)	0
Leukopenia	1 (8)	0	2 (13)	0	2 (13)	0	1 (7)	0	6 (11)	0
Lymphopenia	1 (8)	0	1 (7)	0	3 (20)	0	1 (7)	0	6 (11)	0
Peripheral sensory neuropathy	0	0	1 (7)	0	4 (27)	0	1 (7)	0	6 (11)	0
Pruritus	0	0	2 (13)	0	4 (27)	0	0	0	6 (11)	0
Dizziness	1 (8)	0	1 (7)	0	1 (7)	0	2 (14)	0	5 (9)	0
Neutropenia	2 (17)	0	1 (7)	0	1 (7)	1 (7)	1 (7)	1 (7)	5 (9)	2 (4)
Platelet count decreased	2 (17)	1 (8)	1 (7)	0	2 (13)	0	0	0	5 (9)	1 (2)
Pyrexia	1 (8)	0	1 (7)	0	2 (13)	0	1 (7)	0	5 (9)	0
Tinnitus	1 (8)	0	4 (27)	0	0	0	0	0	5 (9)	0
Hypoesthesia	0	0	0	0	2 (13)	0	2 (14)	0	4 (7)	0
Hypomagnesemia	2 (17)	0	1 (7)	1 (7)	1 (7)	0	0	0	4 (7)	1 (2)
Neutrophil count decreased	2 (17)	1 (8)	0	0	2 (13)	1 (7)	0	0	4 (7)	2 (4)
Cough	0	0	2 (13)	0	0	0	0	0	3 (5)	0
Headache	0	0	0	0	3 (20)	0	0	0	3 (5)	0
Pain in extremity	0	0	0	0	3 (20)	0	0	0	3 (5)	0
Rash maculopapular	1 (8)	0	0	0	2 (13)	2 (13)	0	0	3 (5)	2 (4)
Acute renal failure	0	0	1 (7)	1 (7)	0	0	2 (14)	2 (14)	3 (5)	3 (5)
Thrombocytopenia	2 (17)	1 (8)	0	0	0	0	1 (7)	1 (7)	3 (5)	2 (4)
WBC count decreased	2 (17)	1 (8)	0	0	1 (7)	1 (7)	0	0	3 (5)	2 (4)
Dry skin	0	0	2 (13)	0	0	0	0	0	2 (4)	0
Epistaxis	0	0	0	0	2 (13)	0	0	0	2 (4)	0
Influenza-like illness	0	0	0	0	2 (13)	0	0	0	2 (4)	0
Musculoskeletal discomfort	0	0	0	0	2 (13)	0	0	0	2 (4)	0
Musculoskeletal pain	0	0	0	0	2 (13)	0	0	0	2 (4)	0

NOTE. Data are based on a September 2014 database lock. Table includes events reported between first dose date and 100 days after the last dose of study drug. No grade 5 events were reported. The causal relationship (related or not related) between study drug and AEs was determined by the investigator. Some patients had more than one AE.

Abbreviations: AE, adverse event; Carb, carboplatin; Cis, cisplatin; Gem, gemcitabine; NSCLC, non–small-cell lung cancer; Pac, paclitaxel; Pem, pemetrexed; PT-DC, platinum-based doublet chemotherapy.

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Table 3. Treatment-Related Select AEs Reported in Patients With Advanced NSCLC Treated With Nivolumab Plus PT-DC

	No. of Patients (%)									
	Nivolumab 10 mg/kg						Nivolumab 5 mg/kg			
	Gem-Cis (n = 12)		Pem-Cis (n = 15)		Pac-Carb (n = 15)		Pac-Carb (n = 14)		All Patients (N = 56)	
Select AE Category	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Skin	2 (17)	0	6 (40)	0	6 (40)	2 (13)	6 (43)	1 (7)	20 (36)	3 (5)
Rash	1 (8)	0	5 (33)	0	4 (27)	0	5 (36)	1 (7)	15 (27)	1 (2)
Pruritus	0	0	2 (13)	0	4 (27)	0	0	0	6 (11)	0
Rash maculopapular	1 (8)	0	0	0	2 (13)	2 (13)	0	0	3 (5)	2 (4)
Erythema	0	0	1 (7)	0	0	0	0	0	1 (2)	0
Rash pruritic	0	0	0	0	0	0	1 (7)	0	1 (2)	0
GI	2 (17)	0	3 (20)	1 (7)	5 (33)	1 (7)	3 (21)	0	13 (23)	2 (4)
Diarrhea	2 (17)	0	2 (13)	0	5 (33)	1 (7)	3 (21)	0	12 (21)	1 (2)
Colitis	0	0	1 (7)	1 (7)	1 (7)	0	0	0	2 (4)	1 (2)
Hypersensitivity/infusion reaction	1 (8)	0	6 (40)	1 (7)	6 (40)	0	0	0	13 (23)	1 (2)
Hypersensitivity	1 (8)	0	3 (20)	1 (7)	4 (27)	0	0	0	8 (14)	1 (2)
Infusion-related reaction	0	0	4 (27	0	2 (13)	0	0	0	6 (11)	0
Renal	1 (8)	0	3 (20)	1 (7)	1 (7)	0	3 (21)	2 (14)	8 (14)	3 (5)
Blood creatinine increased	1 (8)	0	1 (7)	0	1 (7)	0	1 (7)	0	4 (7)	0
Acute renal failure	0	0	1 (7)	1 (7)	0	0	2 (14)	2 (14)	3 (5)	3 (5)
Allergic nephritis	0	0	1 (7)	1 (7)	0	0	1 (7)	1 (7)	2 (4)	2 (4)
Blood urea increased	0	0	0	0	0	0	1 (7)	0	1 (2)	0
Creatinine renal clearance decreased	0	0	1 (7)	0	0	0	0	0	1 (2)	0
Renal failure	0	0	0	0	0	0	1 (7)	0	1 (2)	0
Tubulointerstitial nephritis	0	0	1 (7)	0	0	0	0	0	1 (2)	0
Pulmonary	2 (17)	1 (8)	3 (20)	2 (13)	0	0	2 (14)	1 (7)	7 (13)	4 (7)
Pneumonitis	2 (17)	1 (8)	3 (20)	2 (13)	0	0	2 (14)	1 (7)	7 (13)	4 (7)
Endocrine	2 (17)	0	1 (7)	0	0	0	1 (7)	0	4 (7)	0
Hypothyroidism	1 (8)	0	0	0	0	0	1 (7)	0	2 (4)	0
Blood corticotropin decreased	0	0	1 (7)	0	0	0	0	0	1 (2)	0
Blood TSH increased	1 (8)	0	0	0	0	0	0	0	1 (2)	0
Hyperthyroidism	1 (8)	0	0	0	0	0	0	0	1 (2)	0
Hepatic	0	0	1 (7)	0	0	0	0	0	1 (2)	0
ALT increased	0	0	1 (7)	0	0	0	0	0	1 (2)	0
AST increased	0	0	1 (7)	0	0	0	0	0	1 (2)	0

NOTE. Data are based on a September 2014 database lock. Table includes events reported between first dose date and 100 days after the last dose of study drug. No grade 5 events were reported. The causal relationship (related or not related) between study drug and AEs was determined by the investigator. Some patients had more than one AE.

Abbreviations; AE, adverse event; Carb, carboplatin; Cis, cisplatin; Gem, gemcitabine; NSCLC, non–small-cell lung cancer; Pac, paclitaxel; Pem, pemetrexed; PT-DC, platinum-based doublet chemotherapy; TSH, thyroid-stimulating hormone.

of any grade were fatigue, nausea, decreased appetite, and alopecia. The most common (≥ 5% of patients) treatment-related grade 3 or 4 AEs were pneumonitis, fatigue, and acute renal failure. A greater proportion of patients reported onset of treatment-related AEs (any grade and grade 3 or 4) during the combination period (95% [53 of 56 patients] and 38% [21 of 56 patients], respectively) than during nivolumab monotherapy (61% [30 of 49 patients] and 16% [eight of 49 patients], respectively; Data Supplement).

The most frequently observed categories of select AEs were skin, GI, renal, and pulmonary (Table 3). Hypersensitivity/infusion reactions occurred in 23% of patients, all of whom received nivolumab 10 mg/kg plus gemcitabine-cisplatin, pemetrexed-cisplatin, or paclitaxel-carboplatin. A greater proportion of patients reported onset of treatment-related select AEs during the combination period (2% to 29% across categories; Data Supplement) than during nivolumab monotherapy (2% to 12% across categories; Data Supplement).

Treatment-related AEs led to discontinuation of all study therapy in 21% of patients (12 of 56 patients), including 33% of patients (five of 15 patients) in the nivolumab 10 mg/kg plus pemetrexed-cisplatin arm, 29% of patients (four of 14 patients) in the nivolumab 5 mg/kg plus paclitaxel-carboplatin arm, 13% of patients (two of 15 patients) in the nivolumab 10 mg/kg plus paclitaxel-carboplatin arm, and 8% of patients (one of 12 patients) in the nivolumab 10 mg/kg plus gemcitabine-cisplatin arm (Data Supplement). Grade 3 or 4 treatment-related AEs led to discontinuation in 14% of patients (eight of 56 patients), most commonly as a result of pneumonitis and acute renal failure (5% [n = 3] each). Of the patients who discontinued treatment as a result of treatment-related AEs, most (10 of 12 patients) discontinued during the nivolumab monotherapy maintenance period (Data Supplement). All discontinuations as a result of treatment-related pneumonitis occurred during nivolumab monotherapy. At the time of analysis, 37 patients had died. No treatment-related deaths were reported.

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Table 4. Efficacy End Points in Patients With Advanced NSCLC Treated With Nivolumab Plus PT-DC

End Point	Nivolumab 10 mg/kg			Nivolumab 5 mg/kg
	Gem-Cis (n = 12)	Pem-Cis (n = 15)	Pac-Carb (n = 15)	Pac-Carb (n = 14)
Confirmed ORR,* No. (%; 95% CI)	4 (33; 10 to 65)	7 (47; 21 to 73)	7 (47; 21 to 73)	6 (43; 18 to 71)
Confirmed DCR,† No. (%; 95% CI)	11 (92; 61.5 to 99.8)	14 (93; 68.1 to 99.8)	11 (73; 44.9 to 92.2)	12 (86; 57.2 to 98.2)
Ongoing responders,‡ No. (%)	1 (25)	2 (29)	3 (43)	4 (67)
BOR, No. (%)§				
Confirmed CR	1 (8)	0	0	0
Confirmed PR	3 (25)	7 (47)	7 (47)	6 (43)
SD	7 (58)	7 (47)	4 (27)	6 (43)
SD > 21 weeks‖	1 (8)	5 (33)	1 (7)	1 (7)
PD	0	0	4 (27)	1 (7)
Unable to determine	1 (8)	1 (7)	0	1 (7)
Estimated median DOR,¶ months (95% CI)	10.3 (4.1 to 13.0)	5.8 (3.0 to —)	5.5 (2.8 to —)	19.6 (5.1 to —)
Median PFS, months (range)	5.7 (0.02+-14.1)	6.8 (0.9+-24.6+)	4.8 (0.7-28.7+)	7.1 (0.02+-24.8+)
PFS rate at 24 weeks,# % (95% CI)	51 (19 to 76)	71 (39 to 88)	38 (14 to 61)	51 (21 to 75)
Median OS, months (range)	11.6 (4.5-33.3)	19.2 (7.6-35.1+)	14.9 (3.2-34.2+)	NR (8.8-30.1+)
1-year OS rate, % (95% CI)	50 (21 to 74)	87 (56 to 96)	60 (32 to 80)	86 (54 to 96)
2-year OS rate, % (95% CI)	25 (6 to 50)	33 (12 to 56)	27 (8 to 50)	62 (32 to 82)

NOTE. Data for response and PFS are based on a September 2014 database lock. Data for OS are based on a March 2015 database lock. Plus symbol indicates a censored value.

Abbreviations: BOR, best overall response; Carb, carboplatin; Cis, cisplatin; CR, complete response; DCR, disease control rate; DOR, duration of response; Gem, gemcitabine; NR, not reached as a result of insufficient number of events and/or follow-up; NSCLC, non–small-cell lung cancer; ORR, objective response rate; OS, overall survival; Pac, paclitaxel; PR, partial response; PD, progressive disease; PFS, progression-free survival; PT-DC, platinum-based doublet chemotherapy; SD, stable disease.

*Includes patients with initial observations of CR and PR that were subsequently confirmed by repeat scans performed no earlier than 4 weeks after the original observation.

†Includes patients with initial observations of CR and PR that were subsequently confirmed by repeat scans performed no earlier than 4 weeks after the original observation and patients with BOR of SD.

‡Includes patients with confirmed CR or PR who neither experienced progression nor died within 100 days of last nivolumab dose.

§Tumor assessments up to initial disease progression or initiation of subsequent anticancer therapy, whichever occurred first, were considered for BOR assessment.

‖The 21-week time point was chosen on the basis of the timing of tumor assessments.

¶Time from first response to documented progression, or death within 100 days of last nivolumab dose, or last tumor assessment before subsequent therapy (for censored data). Estimated median DORs were determined from Kaplan-Meier curves.

#PFS rate was defined as the probability of a patient remaining progression free and alive up to 24 weeks.

Response and Tumor Kinetics

Across treatment arms, confirmed ORRs ranged from 33% to 47% (Table 4). One patient in the nivolumab 10 mg/kg plus gemcitabine-cisplatin arm achieved a complete response. An additional 27% to 58% of patients had BOR of stable disease (SD), with the highest rate observed for nivolumab 10 mg/kg plus gemcitabine-cisplatin. Across arms, 7% to 33% of patients had SD lasting ≥ 21 weeks. Progressive disease was infrequent, and no patients in the nivolumab 10 mg/kg plus gemcitabine-cisplatin or nivolumab 10 mg/kg plus pemetrexed-cisplatin groups had PD as their BOR. One patient in the nivolumab 5 mg/kg plus paclitaxel-carboplatin arm exhibited a nonconventional immune-related response, with a 59% maximum reduction in target lesions in the presence of a new lesion. Among responders, 71% (17 of 24 patients) had responded by week 10, and 42% of responses (10 of 24 patients) were ongoing after a median follow-up time of 19.0 months (range, 3.2 to 29.7 months; Fig 1A). Of the 12 patients who discontinued treatment as a result of treatment-related AEs, seven (58%) had partial responses with DORs ranging from 3.3+ to 27.4+ months. Reductions in tumor burden were observed across arms (Figs 1B and 1C).

PFS and OS

The 24-week PFS rate ranged from 38% to 71% across arms, with median PFS time ranging from 4.8 to 7.1 months (Table 4, Fig 2A). Median OS time for the three nivolumab 10 mg/kg plus PT-DC arms ranged from 11.6 to 19.2 months but was not reached in the nivolumab 5 mg/kg plus paclitaxel-carboplatin arm (Table 4). At the time of analysis, 57% of patients (eight of 14 patients) treated with nivolumab 5 mg/kg plus paclitaxel-carboplatin were alive, with a median follow-up time of more than 2 years. Across treatment arms, 1- and 2-year OS rates ranged from 50% to 87% and 25% to 62%, respectively (Table 4, Fig 2B).

Efficacy by PD-L1 Expression

Tumor PD-L1 expression was not quantifiable in 21% of patients (12 of 56 patients), either because of suboptimal tissue amount or quality (eg, as a result of no or too few tumor cells, improper fixation, or sectioning artifacts; n = 10) or because no tumor tissue specimen was available for assessment (n = 2). Of the 44 patients (79%) with known PD-L1 expression, 52% (23 of 44 patients) had ≥ 1% PD-L1 expression and 48% (21 of 44 patients) had less than 1% PD-L1 expression (Data Supplement). Confirmed ORRs were 48% (11 of 23 patients) and 43% (nine of 21 patients) for patients with ≥ 1% and less than 1% tumor PD-L1 expression, respectively. Among responders, median DOR was similar for patients with ≥ 1% (6.3 months) and less than 1% (5.8 months) tumor PD-L1 expression. No clear association could be discerned between PD-L1 expression and PFS or OS (Data Supplement), including assessments of higher expression levels of PD-L1 (data not shown).

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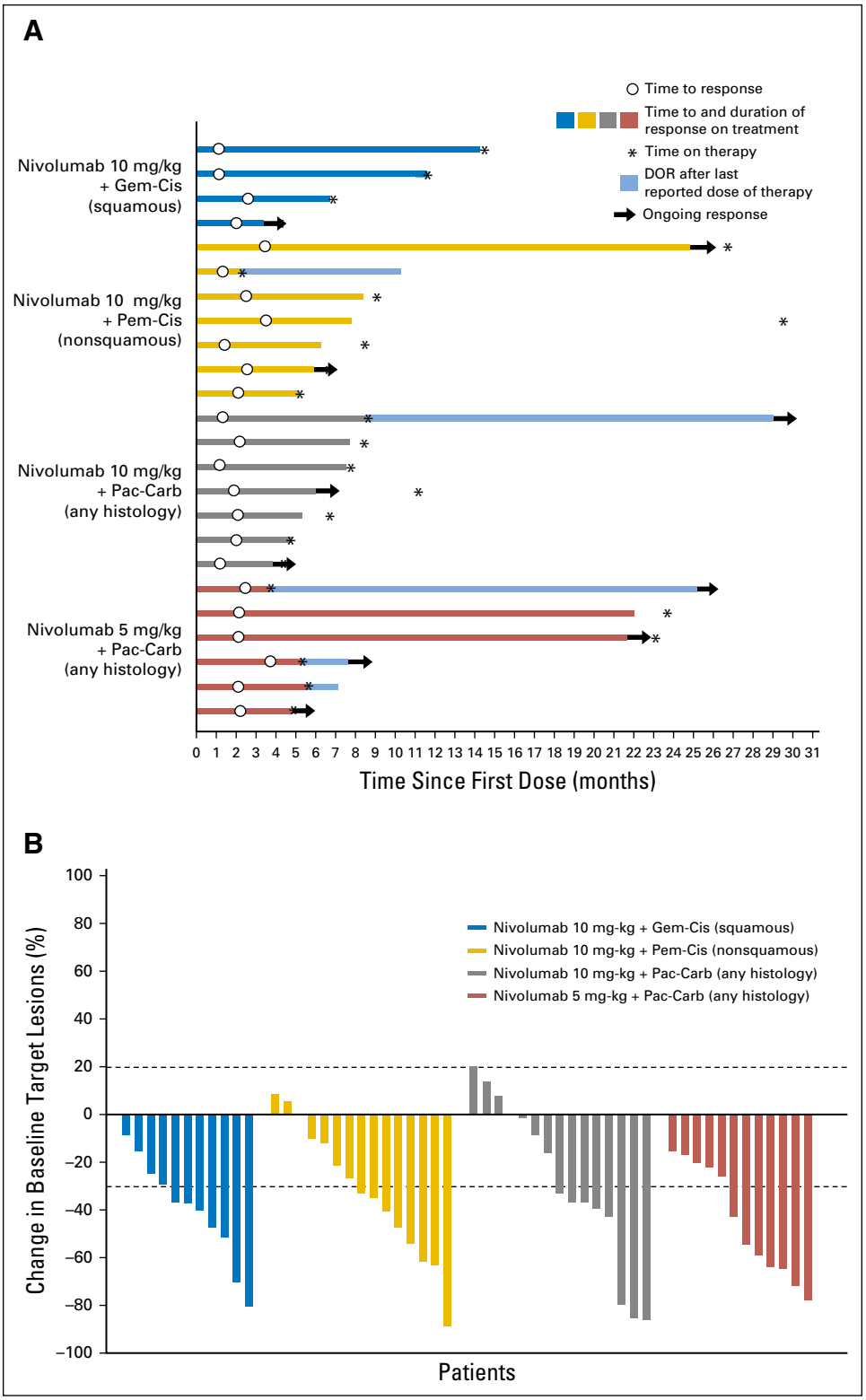

Fig 1. Characteristics of objective response in patients with advanced non–small-cell lung cancer treated with nivolumab plus platinum-based doublet chemotherapy. Data are based on a September 2014 database lock. (A) Time to and duration of response (DOR). (B) Best percent change in target lesion tumor burden from baseline. Only includes patients with baseline target lesion and one or more post-baseline target lesion assessments with non-missing value (gemcitabine [Gem]-cisplatin [Cis], n = 11; pemetrexed [Pem]-Cis, n = 15; nivolumab 10 mg/kg plus paclitaxel [Pac]-carboplatin [Carb], n = 15; nivolumab 5 mg/kg plus Pac-Carb, n = 13). Maximum percent reduction in target lesion tumor burden from baseline across all tumor assessments before subsequent therapy (including after Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 progression assessments) is used. Positive change in tumor burden indicates tumor growth; negative change in tumor burden indicates tumor reduction. Horizontal lines denote 30% decrease and 20% increase. Not all reductions of 30% or greater from baseline are partial responses. (C) Percent change in target lesion tumor burden from baseline over time. Only includes patients with baseline target lesion and one or more postbaseline target lesion assessments with nonmissing value (nivolumab 10 mg/kg plus Gem-Cis, n = 11; nivolumab 10 mg/kg plus Pem-Cis, n = 15; nivolumab 10 mg/kg plus Pac-Carb, n = 15; nivolumab 5 mg/kg plus Pac-Carb, n = 13). Horizontal lines denote 30% decrease, 20% increase, and no change. Plus symbols indicate first appearance of new lesion.

Efficacy by Histology, Smoking History, and EGFR *and* KRAS *Mutation Status*

Confirmed ORRs and PFS were similar between patients with squamous and nonsquamous NSCLC (Data Supplement). However, median DOR was longer for patients with squamous histology than those with nonsquamous histology. Conversely, median OS was longer and the 1-year OS rate higher for patients with nonsquamous versus squamous NSCLC. A trend toward higher ORRs and longer PFS was noted for patients who had a history of smoking (Data Supplement). Among patients with nonsquamous

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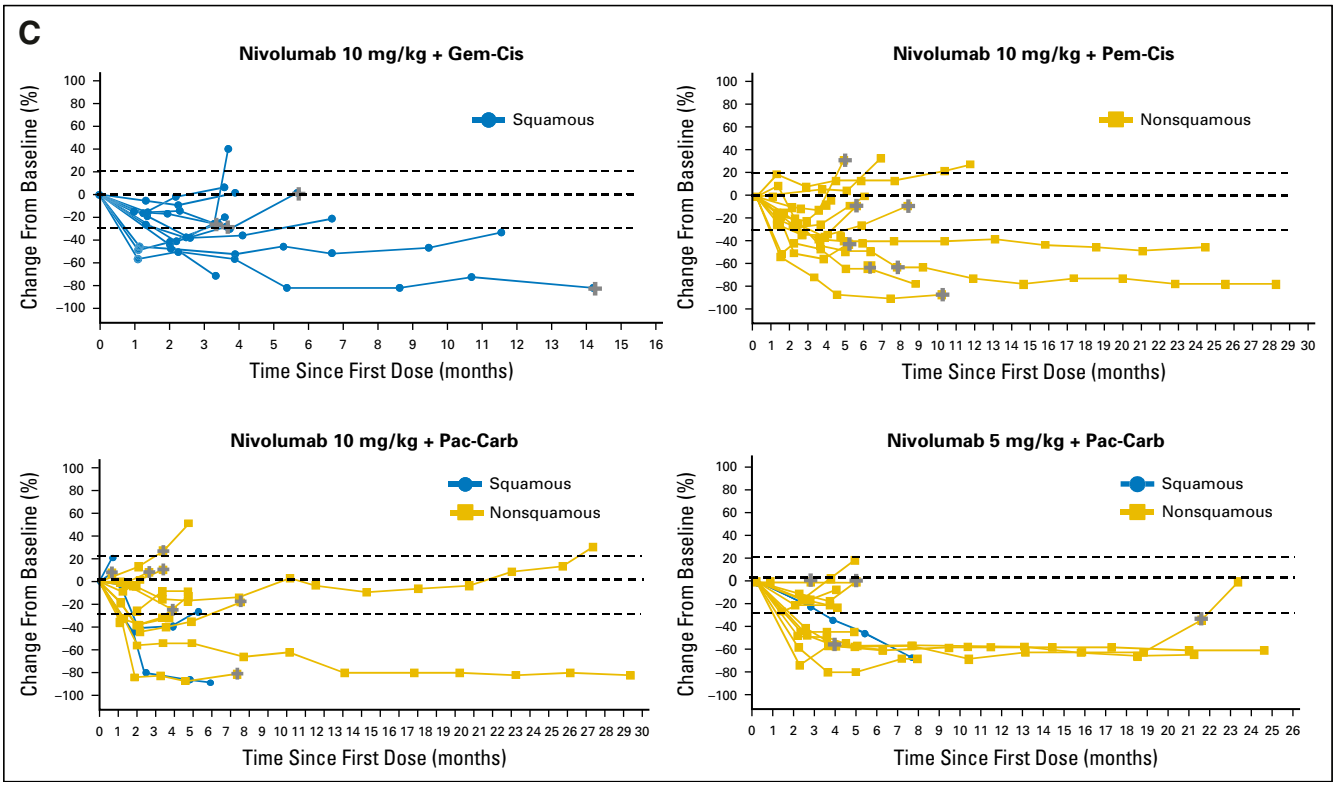

Fig 1. (continued).

NSCLC, responses were noted regardless of *EGFR* or *KRAS* mutation status (Data Supplement). Median PFS and OS times were shorter with *EGFR*- or *KRAS*-mutant versus wild-type tumors. However, 1-year OS rates were similar between patients with *EGFR*- or *KRAS*-mutant tumors and wild-type tumors.

DISCUSSION

For the past several decades, PT-DC has been the standard of care for first-line therapy in advanced NSCLC. However, most patients do not survive for more than 1 year, and limited treatment advances have been made in squamous NSCLC.[5,31] The immunogenic properties of chemotherapy[13,14] and pressing need for improved therapeutic regimens provide a good rationale for combining PT-DC with immunotherapy. Results from this trial suggest that nivolumab plus PT-DC may improve outcomes and extend survival of patients with advanced NSCLC in the first-line setting.

In this study, the most common toxicities reported for the combination were those anticipated with PT-DC alone. The observed frequencies of treatment-related grade 3 or 4 nonhematologic toxicities, such as fatigue and nausea (0% to 13% and 0% to 7%, respectively), are consistent with those previously reported for paclitaxel-carboplatin (8% and 0% to 9%, respectively), pemetrexed-cisplatin (6.7% and 7.2%, respectively), and gemcitabine-cisplatin (4.9% and 1% to 37%, respectively).[2,4-6] Furthermore, fewer than 10% of patients experienced treatment-related grade 3 or 4 leukopenia and anemia, two hematologic toxicities commonly reported with PT-DC (4.8% to 26% and 0% to 27%, respectively).[2,4-6] The observed frequencies of immune-related AEs affecting the skin, GI, renal, and pulmonary organs were greater than expected with single-agent nivolumab (combination therapy *v* monotherapy: 36% *v* 25%, 23% *v* 12%, 14% *v* 0%, and 13% *v* 6%, respectively).[23] However, these treatment-related AEs, including pneumonitis, were effectively managed with corticosteroids or infliximab and did not lead to any deaths.

Overall, 21% of patients discontinued treatment as a result of treatment-related AEs; most discontinuations (10 of 12) occurred during nivolumab monotherapy. Most treatment-related AEs reported during combination cycles were those commonly associated with PT-DC (eg, fatigue, nausea, decreased appetite) and were managed by chemotherapy dose delays and reductions, rather than discontinuation. Chemotherapy and nivolumab are associated with a risk of pneumonitis; however, discontinuation as a result of treatment-related pneumonitis occurred only during nivolumab monotherapy. These results may suggest that corticosteroid premedication for chemotherapy during the combination cycles prevented or partially treated pneumonitis, which worsened during nivolumab monotherapy when there was no regular corticosteroid exposure.

Confirmed ORRs with nivolumab plus PT-DC ranged from 33% to 47% across arms, which compares favorably to previously reported rates of 15% to 32% for PT-DC alone.[1-6] Clinical benefit was further reflected by high SD rates (27% to 58%), low frequencies of PD as BOR (0% to 27%), and potentially longer median PFS (4.8 to 7.1 months) relative to PT-DC alone (SD, 18% to 40%; PD, 18% to 49%; median PFS, 4.0 to 5.1 months).[2,4,6]

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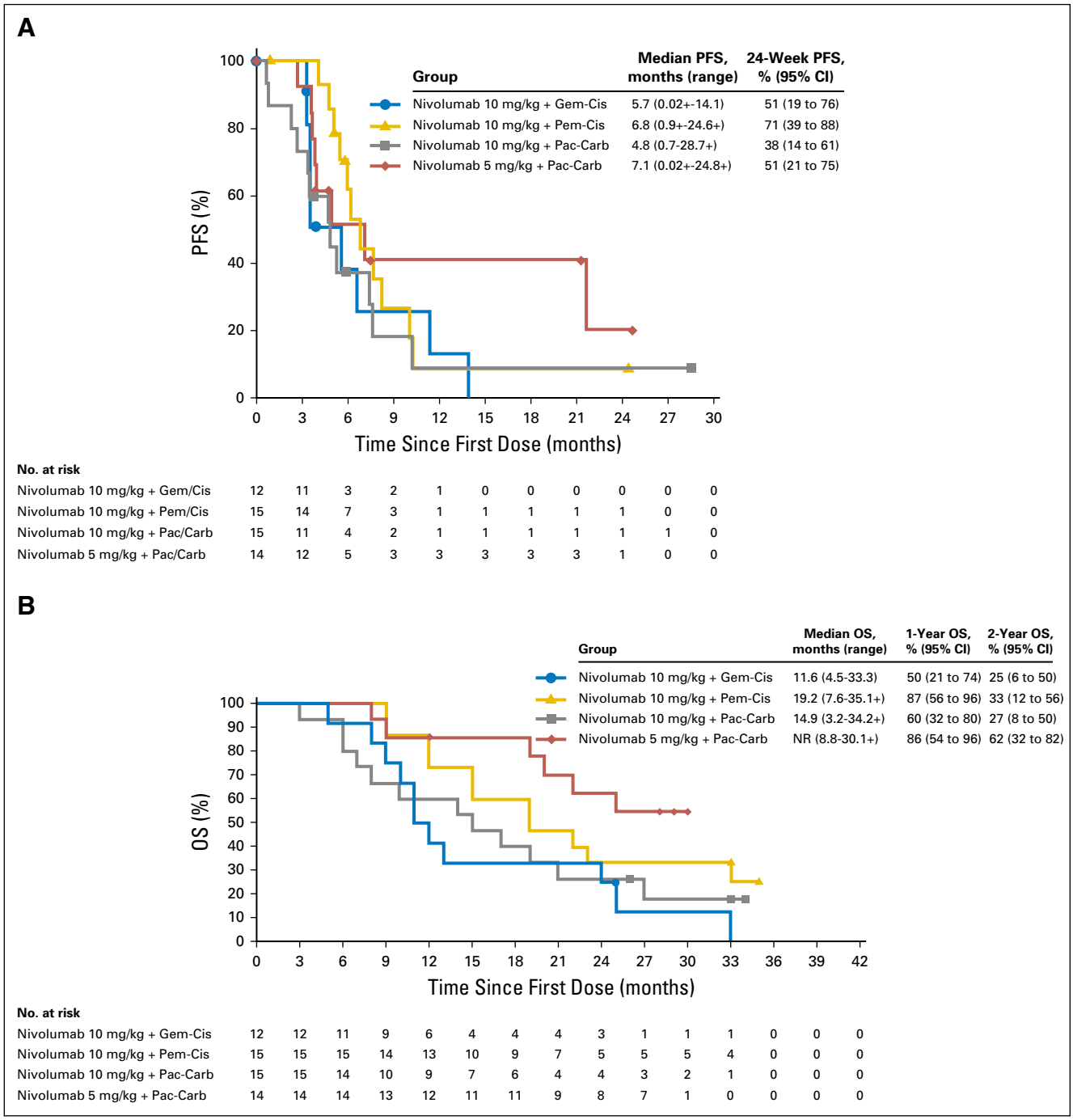

Fig 2. Survival outcomes in patients with advanced non–small-cell lung cancer treated with nivolumab plus platinum-based doublet chemotherapy. (A) Progression-free survival (PFS). Data for PFS are based on a September 2014 database lock. Symbols denote censored observations. (B) Overall survival (OS). Data for OS are based on a March 2015 database lock. Median OS was not reached (NR) for the nivolumab 5 mg/kg plus paclitaxel (Pac)-carboplatin (Carb) group as a result of insufficient number of events and/or follow-up. Symbols denote censored observations. Cis, cisplatin; Gem, gemcitabine; Pem, pemetrexed.

Furthermore, median OS was longer than expected for PT-DC alone (8.1 to 10.3 months),[1-6] ranging from 11.6 to 19.2 months across the nivolumab 10 mg/kg plus PT-DC arms. OS for the nivolumab 5 mg/kg plus paclitaxel-carboplatin arm was particularly notable; median OS was not reached (range, 8.8 to 30.1+ months), and 57% of patients (eight of 14 patients) were still alive after a median follow-up time of more than 2 years. Pharmacokinetic modeling suggests that nivolumab 5 mg/kg every 3 weeks results in sustained exposure between treatments, equivalent to nivolumab 3 mg/kg every 2 weeks.[17] Although sample sizes were small, 1-year OS rates (50% to 87%) seemed similar to that seen with nivolumab monotherapy (73%) in CheckMate 012.[32] It is unclear at this time whether nivolumab plus PT-DC offers improved long-term OS benefit compared with nivolumab monotherapy. However, survival data

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with nivolumab 5 mg/kg every 3 weeks in combination with chemotherapy are encouraging and will be further explored in a phase III trial.

Recently, anti–PD-1/PD-L1 agents have demonstrated greater efficacy in patients whose tumors express PD-L1.[20,33-35] Nevertheless, the absence or low expression of PD-L1 does not preclude response to or survival benefit from nivolumab.[19,20,23,36] In this study, equivalent responses were noted across tumor PD-L1 expression levels with no discernible association between PD-L1 expression and PFS or OS. Although limited by small sample sizes, these data may suggest that PD-L1 expression is not associated with response to nivolumab or that its predictive value for nivolumab benefit may be attenuated or negated in combination with PT-DC. Consistent with results of nivolumab as first-line monotherapy,[23] responses were observed regardless of histologic subtype or mutation status. However, higher clinical activity was observed among patients with a history of smoking, which may relate to the higher mutational load in smoking-associated lung cancer, leading to more tumor neoantigens and increased immunogenicity.[37-39]

In summary, our results suggest that the safety profile of nivolumab plus PT-DC can be managed using established safety guidelines. Despite the small sample sizes of the individual cohorts and patient selection for phase I studies, the clinical activity of nivolumab plus PT-DC, and of nivolumab 5 mg/kg plus paclitaxel-carboplatin in particular, is promising relative to historical results with PT-DC alone. Collectively, our results suggest that nivolumab plus PT-DC may provide benefit beyond single-modality chemotherapy and may represent a treatment option for patients with rapidly progressing disease or whose tumors do not express PD-L1. Further randomized trials of nivolumab plus PT-DC in first-line advanced NSCLC are warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Nivolumab in Combination With Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non–Small-Cell Lung Cancer

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