ORIGINAL ARTICLE

Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort

Neal E. Ready, MD, PhD,[a,*] Patrick A. Ott, MD, PhD,[b] Matthew D. Hellmann, MD,[c,d] Jon Zugazagoitia, MD, PhD,[e] Christine L. Hann, MD, PhD,[f] Filippo de Braud, MD,[g,h] Scott J. Antonia, MD, PhD,[i] Paolo A. Ascierto, MD,[j] Victor Moreno, MD, PhD,[k] Akin Atmaca, MD,[l] Stefania Salvagni, MD,[m] Matthew Taylor, MD,[n] Asim Amin, MD, PhD,[o] D. Ross Camidge, MD, PhD,[p] Leora Horn, MD, MSc,[q] Emiliano Calvo, MD, PhD,[r] Ang Li, MS,[s] Wen Hong Lin, MD, MSc,[s] Margaret K. Callahan, MD, PhD,[c] David R. Spigel, MD[t]

[a]*Duke University Medical Center, Durham, North Carolina*
[b]*Dana Farber Cancer Institute, Boston, Massachusetts*

*Corresponding author.

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Address correspondence to: Neal E. Ready, MD, PhD, Duke University Medical Center, 10 Duke Medicine Circle, Durham, North Carolina 27710. E-mail: neal.ready@duke.edu

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[c]Memorial Sloan-Kettering Cancer Center, New York, New York
[d]Weill Cornell Medical College, New York, New York
[e]University Hospital 12 de Octubre, Madrid, Spain
[f]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland
[g]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan
[h]University of Milan, Milan, Italy
[i]H. Lee Moffitt Cancer Center, Tampa, Florida
[j]Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy
[k]START Madrid - FJD, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain
[l]Department of Oncology and Hematology, Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt, Germany
[m]Policlinico S.Orsola-Malpighi, Azienda Ospedaliero Universitaria, Bologna, Italy
[n]Oregon Health & Science University, Portland, Oregon
[o]Levine Cancer Institute, Atrium Healthcare System, Charlotte, North Carolina
[p]University of Colorado Denver, Aurora, Colorado
[q]Vanderbilt Ingram Cancer Center, Nashville, Tennessee
[r]START Madrid - CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain
[s]Bristol-Myers Squibb, Lawrenceville, New Jersey
[t]Sarah Cannon Research Institute/Tennessee Oncology Nashville, Nashville, Tennessee

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ABSTRACT

Introduction: Nivolumab monotherapy is approved in the United States for third-line or later metastatic small cell lung cancer based on pooled data from nonrandomized and randomized cohorts of the multicenter, open-label, phase 1/2 trial of nivolumab ± ipilimumab (CheckMate 032; NCT01928394). We report updated results, including long-term overall survival (OS), from the randomized cohort.

Methods: Patients with small cell lung cancer and disease progression after one to two prior chemotherapy regimens were randomized 3:2 to nivolumab 3 mg/kg every 2 weeks or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four cycles followed by nivolumab 3 mg/kg every 2 weeks. Patients were stratified by number of prior chemotherapy regimens and treated until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) by blinded independent central review.

Results: Overall, 147 patients received nivolumab and 96 nivolumab plus ipilimumab. Minimum follow-up for ORR/progression-free survival/safety was 11.9 months (nivolumab) and 11.2 months (nivolumab plus ipilimumab). ORR increased with nivolumab plus ipilimumab (21.9% versus 11.6% with nivolumab; odds ratio: 2.12; 95% confidence interval: 1.06–4.26; $p = 0.03$). For long-term OS, minimum follow-up was 29.0 months (nivolumab) versus 28.4 months (nivolumab plus ipilimumab); median (95% confidence interval) OS was 5.7 (3.8–7.6) versus 4.7 months (3.1–8.3). Twenty-four–month OS rates were 17.9% (nivolumab) and 16.9% (nivolumab plus ipilimumab). Grade 3 to 4 treatment-related adverse event rates were 12.9% (nivolumab) versus 37.5% (nivolumab plus ipilimumab), and treatment-related deaths were n =1 versus n = 3, respectively.

Conclusions: Whereas ORR (primary endpoint) was higher with nivolumab plus ipilimumab versus nivolumab, OS was similar between groups. In each group, OS remained encouraging with long-term follow-up. Toxicities were more common with combination therapy versus nivolumab monotherapy.

Keywords: Small cell lung cancer: Nivolumab; Ipilimumab; Programmed death-1 inhibitor; Immunotherapy

Introduction

Patients with recurrent small cell lung cancer (SCLC) have limited treatment options and poor survival.[1] Nivolumab, an anti–programmed death-1 antibody, and ipilimumab, an anti–cytotoxic T-lymphocyte associated protein 4 antibody, are immune checkpoint inhibitors with complementary mechanisms of action. Nivolumab is approved alone or in combination with ipilimumab for the treatment of several types of cancer, including melanoma, renal cell carcinoma, and colorectal cancer.[2-7]

The CheckMate 032 trial (NCT01928394) evaluated nivolumab alone or in combination with ipilimumab in patients with previously treated advanced or metastatic solid tumors, including SCLC.[8] Initial results from a nonrandomized cohort of patients with SCLC and progression after platinum-based chemotherapy showed the antitumor activity of nivolumab monotherapy and nivolumab plus ipilimumab, characterized by durable responses, encouraging survival, and manageable toxicity.[8,9] With a median follow-up of 15.7 months and 21.0 months, respectively, patients receiving nivolumab

monotherapy or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg in the nonrandomized cohort had a 2-year overall survival (OS) rate of 17% and 30%, respectively, and a median duration of response (DOR) of not reached and 11.7 months.[10]

A randomized cohort was subsequently added to assess the clinical activity of nivolumab monotherapy versus nivolumab plus ipilimumab. Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks was selected as the combination regimen for the randomized cohort rather than nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks based on a clinically meaningful increase in response rate in the nonrandomized cohort. Although the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg regimen was associated with higher rates of grade 3 to 4 treatment-related adverse events (TRAEs) in analyses from the nonrandomized cohort, the regimen was tolerable and events manageable with established algorithms[8]; in addition, these doses have been used safely and effectively in patients with melanoma and are approved by the United States Food and Drug Administration (FDA) for use in patients with unresectable or metastatic melanoma.[2,3]

An initial report of the randomized cohort, at a minimum follow-up of 3 months, showed an objective response rate (ORR; primary endpoint) of 12% with nivolumab monotherapy and 21% with nivolumab plus ipilimumab, and 3-month progression-free survival (PFS) rates of 18% and 30%, respectively; however, preliminary OS rates at 3 months were similar between treatment groups.[11]

In addition to these analyses of the randomized cohort, pooled efficacy and safety data for third-line or later nivolumab monotherapy from the nonrandomized and randomized cohorts have been reported with a minimum follow-up of 11.9 months.[12] Based on these data, the FDA approved nivolumab monotherapy for the treatment of metastatic SCLC with progression after platinum-based chemotherapy and at least one other line of therapy.[2]

This paper presents updated efficacy and safety data from the randomized cohort of patients with SCLC, including long-term OS data.

Methods

The methodology of the CheckMate 032 trial has been previously reported.[8]

Patients

The SCLC cohort of CheckMate 032 included patients aged 18 years or older, unselected for programmed death ligand 1 (PD-L1) tumor expression, with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, histologically or cytologically confirmed limited-stage or extensive-stage SCLC at diagnosis, and progressive disease after one or two prior chemotherapy regimens, including a platinum-based regimen as first-line treatment. Patients with active brain metastases or leptomeningeal metastases were excluded; however, patients were eligible if they had brain metastases that had been treated and no magnetic resonance imaging evidence of progression for at least 4 weeks after treatment was completed and within 28 days before the first dose of study drug, or if they had only incidental findings of asymptomatic brain metastases at screening.

Trial Design and Treatment

CheckMate 032 is a multicenter, open-label, phase 1/2 trial in advanced/metastatic solid tumors.[8] Initially, patients with SCLC were treated with nivolumab or one of three dosing regimens of nivolumab combined with ipilimumab (nonrandomized cohort) to assess the safety and appropriate dosing of combination therapy in SCLC.[8] Because encouraging clinical activity was observed, a subsequent randomized cohort was added to confirm this activity of nivolumab versus nivolumab plus ipilimumab. Patients were randomized (3:2 ratio), with stratification by prior treatment lines (one versus two prior chemotherapy regimens), to receive nivolumab 3 mg/kg every 2 weeks or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four cycles, followed by nivolumab 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity.

Endpoints

In the randomized cohort, the primary endpoint was ORR as assessed by blinded independent central review (BICR) per the Response Evaluation Criteria in Solid Tumors, version 1.1.[13] Secondary endpoints were DOR by BICR, PFS by BICR, OS, and safety. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. Events with an outcome of death were reported according to the grade experienced at presentation.

Statistical Analysis

This analysis included data from the randomized cohort only. Efficacy was analyzed as described previously.[8] Tumor mutational burden (TMB) categories (low, medium, or high) were defined according to the baseline tertile of pooled TMB-evaluable patients using whole-exome sequencing from the randomized cohort only.

The database lock was November 6, 2017, for ORR, PFS, and safety, and April 12, 2019, for long-term OS.

Trial Oversight

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, as defined by the International Conference on Harmonization. An institutional review board or independent ethics committee at each participating center approved the study protocol. All patients provided written informed consent. The Bristol-Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

Results

Patients and Treatment

In the randomized SCLC cohort of CheckMate 032, 147 patients initiated treatment with nivolumab and 96 with nivolumab plus ipilimumab between October 21, 2015, and November 30, 2016. Baseline patient characteristics were balanced between the two groups (Table 1).

At the database lock on November 6, 2017, the minimum follow-up for efficacy and safety data was 11.9 months with nivolumab and 11.2 months with nivolumab plus ipilimumab. The median number (range) of doses of nivolumab received as monotherapy was 3 (1–48) doses; in the nivolumab plus ipilimumab group, patients received a median (range) of 2 (1–45) doses of nivolumab and 2 (1–4) doses of ipilimumab. Median cumulative dose of nivolumab was 9.1 mg/kg in the nivolumab group and 2.1 mg/kg in the nivolumab plus ipilimumab group; median cumulative dose of ipilimumab was 6.1 mg/kg. Eight patients (5.4%) in the nivolumab group and eight patients (8.3%) in the nivolumab plus ipilimumab group continued to receive study treatment at

Table 1. Baseline Demographics and Clinical Characteristics

	Nivolumab (n = 147)	Nivolumab + Ipilimumab (n = 96)
Median age, years (range)	63.0 (29-83)	65.0 (41-91)
≥65 years, n (%)	65 (44.2)	49 (51.0)
Male	86 (58.5)	61 (63.5)
Race		
White	134 (91.2)	87 (90.6)
Black/African American	7 (4.8)	5 (5.2)
Asian	2 (1.4)	1 (1.0)
Other	4 (2.7)	3 (3.1)
Prior systemic treatment regimens		
1	97 (66.0)	65 (67.7)
2-3[a]	50 (34.0)	31 (32.3)
First-line platinum sensitivity		
Sensitive[b]	73 (49.7)	55 (57.3)
Resistant[c]	73 (49.7)	40 (41.7)
Unknown	1 (0.7)	1 (1.0)
Smoking status		
Current/former smoker	136 (92.5)	91 (94.8)
Never smoked	10 (6.8)	4 (4.2)
Unknown	1 (0.7)	1 (1.0)
ECOG PS		
0	49 (33.3)	27 (28.1)
1	98 (66.7)	68 (70.8)
Not reported	0	1 (1.0)
Baseline TMB[d]		
All evaluable	99 (67.3)	65 (67.7)
TMB low	32 (32.3)	21 (32.3)
TMB medium	34 (34.3)	22 (33.8)
TMB high	33 (33.3)	22 (33.8)

Values are n (%) unless otherwise stated.
Data are based on a database lock of November 6, 2017.
[a]Although randomization to the randomized cohort was limited to subjects with one or two prior lines of therapy, one patient in each treatment group received three lines of prior therapy.
[b]Progression-free ≥90 days after completion of platinum-based chemotherapy.
[c]Progression-free <90 days after completion of platinum-based chemotherapy.
[d]TMB categories (low, medium, high) were defined according to the baseline tertile of pooled TMB-evaluable patients from the randomized cohort, and percentages calculated based on the total TMB-evaluable population.
ECOG PS, Eastern Cooperative Oncology Group performance status; TMB, tumor mutational burden.

database lock. The most common reason for treatment discontinuation was disease progression in both groups (nivolumab, 80.3%; nivolumab plus ipilimumab, 61.5%) (Supplementary Table 1).

For long-term OS, at the database lock of April 12, 2019, the minimum follow-up was 29.0 months and 28.4 months with nivolumab and nivolumab plus ipilimumab, respectively.

Efficacy

The ORR was 11.6% (95% confidence interval [CI]: 6.9–17.9) in the nivolumab group and 21.9% (95% CI: 14.1–31.5) in the nivolumab plus ipilimumab group (Table 2). The absolute difference in ORR between treatment groups was 10.3% (95% CI: 0.6–20.1), with an odds ratio of 2.12 (95% CI: 1.06–4.26; $p = 0.03$) (Table 2). Median DOR was 15.8 months (95% CI: 7.4–not reached) in the nivolumab group and 10.0 months (95% CI: 6.7–not reached) in the nivolumab plus ipilimumab group. Twelve (70.6%) and 15 (71.4%) responders in the nivolumab and nivolumab plus ipilimumab groups, respectively, had a DOR of at least 6 months, and six (35.3%) and seven (33.3%) responders of at least 12 months (Fig. 1).

The median PFS with nivolumab and nivolumab plus ipilimumab was 1.4 months (95% CI: 1.3–1.4) and 1.5 months (95% CI: 1.4–2.2), respectively. PFS rates at 3 months were 19.8% (95% CI: 13.7–26.8) and 31.6% (95% CI: 22.6–41.0), at 6 months were 15.9% (95% CI: 10.3–22.5) and 22.1% (95% CI: 14.4–30.9), and at 12 months were 9.5% (95% CI: 5.2–15.2) and 11.9% (95% CI: 6.3–19.5) (Fig. 2).

Subsequent systemic cancer therapy was received by 32.0% and 16.7% of patients treated with nivolumab and nivolumab plus ipilimumab, respectively, including chemotherapy (22.4% and 11.5%), experimental drugs (8.8% and 6.3%), and immunotherapy (6.1% and 3.1%).

Among patients who exhibited partial or complete responses, 18% discontinued treatment due to study drug toxicity in the nivolumab group versus 29% in the nivolumab plus ipilimumab group. Among responders, the median number of nivolumab doses was 30 in the nivolumab group versus 12 in the nivolumab plus ipilimumab group; the dose of nivolumab during the first four cycles was also higher in the nivolumab group (3 mg/kg every 2 weeks versus 1 mg/kg every 3 weeks) and the median cumulative dose of nivolumab among responders was 90.1 mg/kg and 32.3 mg/kg, respectively. The median number of ipilimumab doses received among responders in the nivolumab plus ipilimumab group was four, with a median cumulative dose of 12.0 mg/kg.

At the updated database lock for long-term OS, median OS was 5.7 months (95% CI: 3.8–7.6) with nivolumab and 4.7 months (95% CI: 3.1–8.3) with nivolumab plus ipilimumab. The 12- and 24-month OS rates were 30.5% (95% CI: 23.1–38.3) and 17.9% (95% CI: 11.9–24.9) for nivolumab, and 30.2% (95% CI: 21.2–39.6) and 16.9% (95% CI: 10.1–25.3) for nivolumab plus ipilimumab (Fig. 3*A*). Analyses of key patient subgroups showed no significant differences in OS between treatments for any subgroups analyzed, including sex, prior lines of

Table 2. Summary of Tumor Response

Endpoint	Nivolumab (n = 147)		Nivolumab + Ipilimumab (n = 96)
ORR by BICR[a]			
No. of patients	17		21
% of patients (95% CI)	11.6 (6.9-17.9)		21.9 (14.1-31.5)
Difference between groups, % (95% CI)[b,c]		10.3 (0.6-20.1)	
Odds ratio (95% CI)[c,d]		2.12 (1.06-4.26)	
p value[e]		0.03	
Best overall response, n (%)			
Complete response	2 (1.4)		2 (2.1)
Partial response	15 (10.2)		19 (19.8)
Stable disease	25 (17.0)		16 (16.7)
Progressive disease	87 (59.2)		41 (42.7)
Unable to determine	15 (10.2)		17 (17.7)
Not reported	3 (2.0)		1 (1.0)
Median time to response, mo	1.5		1.4

Data are based on a database lock of November 6, 2017.
[a]Per the Response Evaluation Criteria in Solid Tumors version 1.1.
[b]Strata adjusted difference in ORR ([nivolumab + ipilimumab] minus nivolumab) based on Cochran-Mantel-Haenszel method of weighting.
[c]Stratified by number of prior treatment lines (one versus two prior chemotherapy regimens) as for randomization.
[d]Strata adjusted odds ratio (nivolumab + ipilimumab over nivolumab) using Mantel-Haenszel method.
[e]Two-sided *p* value from stratified Cochran-Mantel-Haenszel test.
BICR, blinded independent central review; CI, confidence interval; ORR, objective response rate.

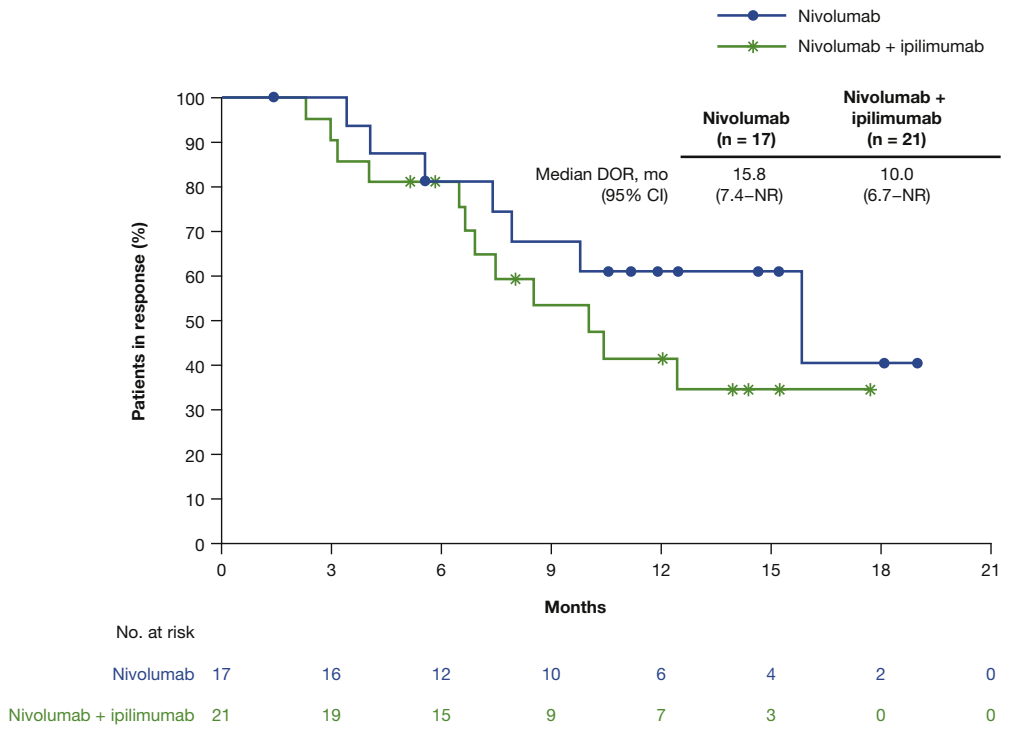


Figure 1. Duration of response. Data are based on a database lock of November 6, 2017. CI, confidence interval; DOR, duration of response; NR, not reached.

therapy, platinum sensitivity, and baseline TMB (Fig. 3*B*). As only 14 patients with nivolumab and 10 patients with nivolumab plus ipilimumab had PD-L1 expression greater than or equal to 1%, an analysis for outcomes by PD-L1 expression was not performed.

Safety

Any-grade TRAEs were reported in 53.7% of patients in the nivolumab group and 68.8% of patients in the nivolumab plus ipilimumab group (Table 3). Grade 3 to 4 TRAEs occurred in 12.9% of patients receiving nivolumab and 37.5% of those receiving nivolumab plus ipilimumab. The most frequent (≥10%) TRAEs of any grade were fatigue (12.2%) with nivolumab, and diarrhea (19.8%), fatigue (18.8%), pruritus (16.7%), and nausea, increased aspartate aminotransferase and decreased appetite (each 10.4%) with nivolumab plus ipilimumab. TRAEs led to discontinuation in 2.7% of patients receiving nivolumab and 13.5% of those receiving nivolumab plus ipilimumab; the majority of these events were grade 3 to 4 and are detailed in Supplementary Table 2. One treatment-related death occurred in the nivolumab group due to pneumonitis, and three in the nivolumab plus ipilimumab group, with one each due to hepatitis, pneumonitis, and encephalitis. In addition, one death was reported with nivolumab plus ipilimumab due to both study treatment toxicity (autoimmune colitis) and disease progression.

Discussion

This report presents a longer follow-up analysis of efficacy and safety data for the nivolumab versus nivolumab plus ipilimumab randomized SCLC cohorts of the CheckMate 032 study, updating previous data reported with a minimum follow-up of 3 months.[11] Nivolumab monotherapy provided durable responses in a subset of patients and was well tolerated as a second- or later-line treatment for recurrent SCLC, consistent with previous observations from the randomized cohort.[11] Furthermore, the efficacy of nivolumab monotherapy in this analysis was similar to that from the pooled nonrandomized and randomized cohorts of patients who received third- or later-line nivolumab monotherapy in CheckMate 032 (ORR, 11.6% versus 11.9%; median DOR, 15.8 months versus 17.9 months; 12-month OS rate, 30.5% versus 28.3%).[12] The combination of nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) significantly improved the primary endpoint of ORR compared with nivolumab monotherapy; however, the combination was associated with increased toxicity, and the higher response rate did not translate into longer PFS or OS. Additionally, no significant benefit in OS was observed with nivolumab plus ipilimumab versus nivolumab in any

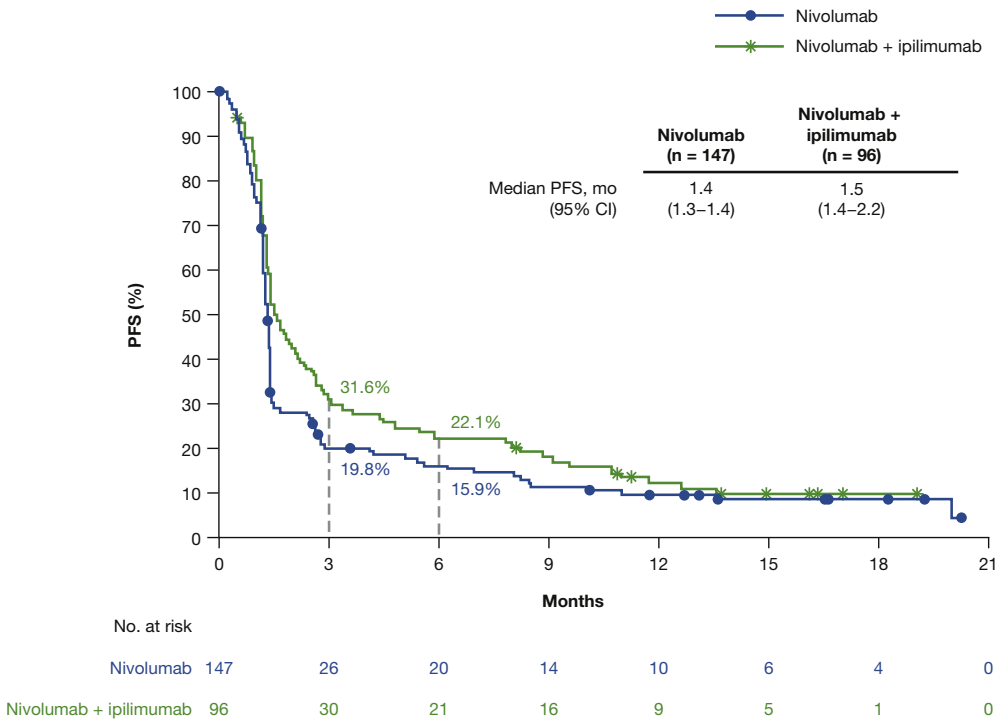


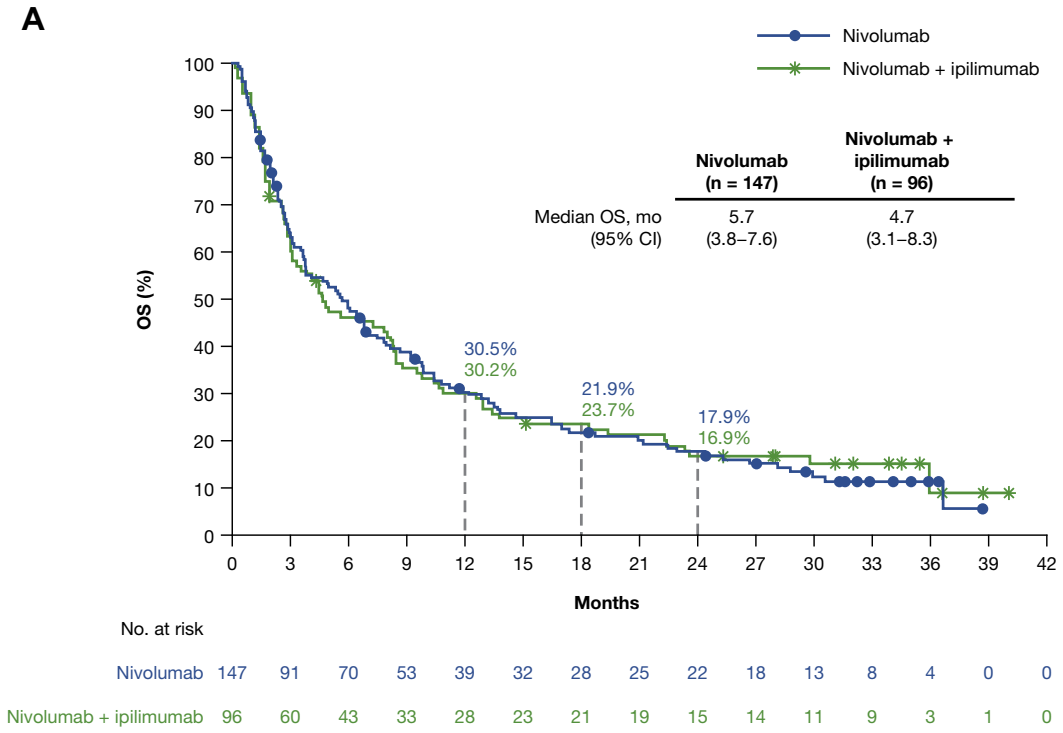
Figure 2. Progression-free survival. Data are based on a database lock of November 6, 2017. CI, confidence interval; mo, months; PFS, progression-free survival.

patient subgroups analyzed, although the 24-month OS rates were clinically meaningful (~18%) in both groups.

The discrepancy between ORR and PFS/OS data at these doses of nivolumab (3 mg/kg) and nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) may be explained by a higher number of treatment discontinuations due to study drug toxicity in the nivolumab plus ipilimumab group (even among responders), and a lower rate of subsequently administered therapies compared to the nivolumab monotherapy group. An apparent early benefit of nivolumab plus ipilimumab in ORR and PFS but shorter DOR compared with nivolumab alone is also consistent with differences in treatment duration; however, whether early discontinuation of nivolumab plus ipilimumab affected the likelihood of disease progression cannot be determined. Other schedules combining nivolumab and ipilimumab in lung cancer have shown better tolerability than the regimen studied in the randomized cohort of CheckMate 032. CheckMate 012, a multi-institutional phase 1 trial in patients with previously untreated advanced NSCLC included treatment arms combining nivolumab with ipilimumab every 3 weeks, every 6 weeks, or every 12 weeks.[14] The nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks regimen was better tolerated than the regimens with ipilimumab every 3 weeks, and was chosen for phase 2/3 development. CheckMate 568, a large phase 2 trial, and CheckMate 227, a large phase 3 trial, found that nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks was tolerable and could be effectively given in patients with NSCLC.[15-17]

Previous analysis of pooled data from the nonrandomized and randomized cohorts of CheckMate 032 explored the effect of TMB on efficacy outcomes in patients with SCLC.[18] This analysis used whole-exome sequencing to determine TMB and grouped patients into tertiles to define categories of high, medium, and low TMB. Results indicated a potential survival benefit from nivolumab plus ipilimumab versus nivolumab monotherapy for patients with a high TMB, whereas for patients with medium or low TMB, survival was similar with nivolumab plus ipilimumab or nivolumab alone. A similar trend was observed in the current analysis of the randomized cohort. However, given the limited sample size and exploratory nature of the TMB analysis, these data should be interpreted with caution.

The safety profile for nivolumab monotherapy was consistent with that seen in pooled data from the randomized and nonrandomized SCLC cohorts.[12] The doses of nivolumab and ipilimumab administered to patients with SCLC in the combination group of the randomized cohort (nivolumab, 1 mg/kg every 2 weeks; ipilimumab, 3 mg/kg every 3 weeks) differ from those being explored



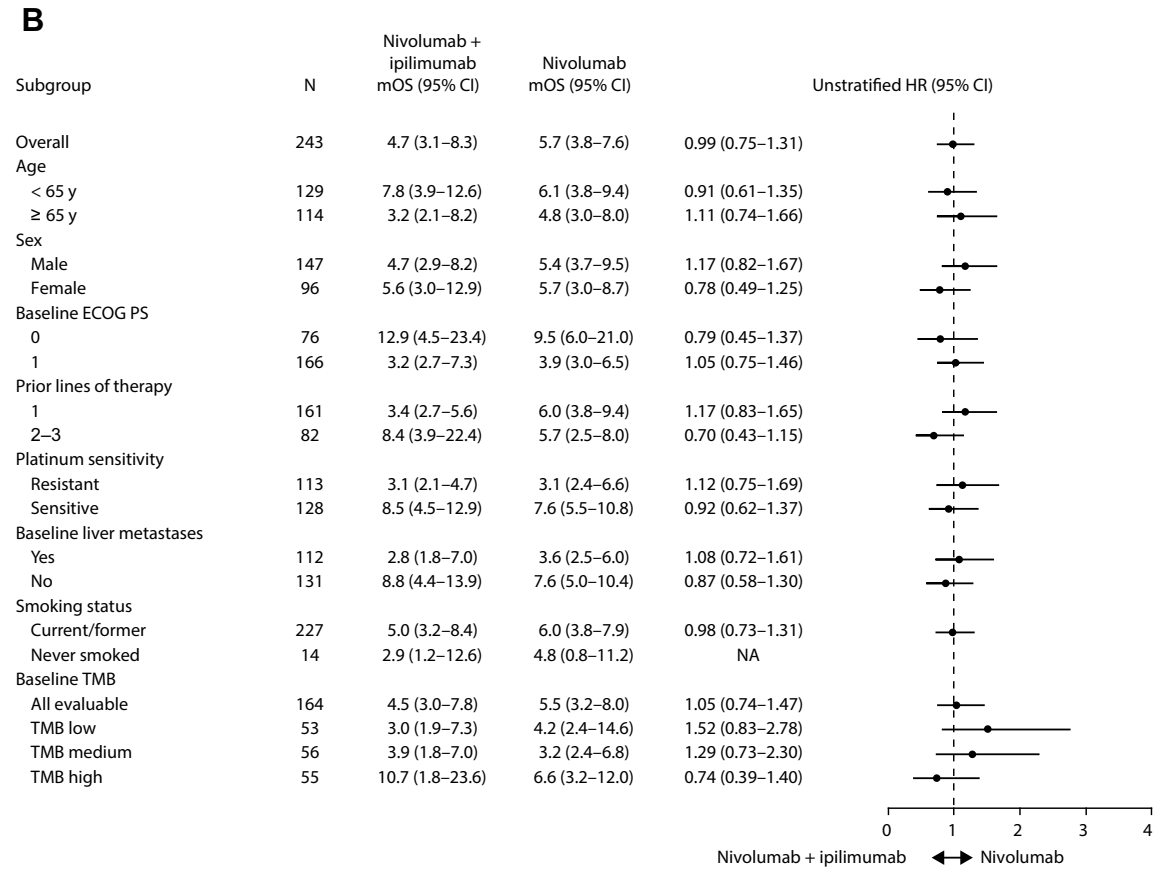


Figure 3. Long-term overall survival in total patient population (*A*) and in selected subgroups of patients (*B*) Data are based on a database lock of April 12, 2019. HRs were not calculated for subgroups with less than 10 patients per treatment group. TMB categories (low, medium, high) were defined according to baseline tertile. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mOS, median overall survival; NA, not available; TMB, tumor mutational burden.

Table 3. Treatment-Related Adverse Events

	Nivolumab (n = 147)		Nivolumab + Ipilimumab (n = 96)	
Event, n (%)	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any event	79 (53.7)	19 (12.9)	66 (68.8)	36 (37.5)
Any serious event	9 (6.1)	8 (5.4)	25 (26.0)	22 (22.9)
Any event leading to discontinuation	4 (2.7)	4 (2.7)	13 (13.5)	11 (11.5)
Most frequent events (≥5% in either group)				
Fatigue	18 (12.2)	1 (0.7)	18 (18.8)	1 (1.0)
Pruritus	14 (9.5)	0	16 (16.7)	0
Arthralgia	9 (6.1)	0	6 (6.3)	0
Infusion-related reaction	9 (6.1)	0	0	0
Rash	8 (5.4)	1 (0.7)	6 (6.3)	1 (1.0)
Nausea	7 (4.8)	0	10 (10.4)	0
AST increased	7 (4.8)	2 (1.4)	10 (10.4)	5 (5.2)
Diarrhea	6 (4.1)	0	19 (19.8)	5 (5.2)
Maculopapular rash	6 (4.1)	0	9 (9.4)	3 (3.1)
Hypothyroidism	6 (4.1)	0	8 (8.3)	0
Decreased appetite	6 (4.1)	1 (0.7)	10 (10.4)	0
Asthenia	5 (3.4)	0	5 (5.2)	0
Lipase increased	5 (3.4)	4 (2.7)	5 (5.2)	5 (5.2)
ALT increased	4 (2.7)	0	9 (9.4)	5 (5.2)
Pneumonitis	3 (2.0)	3 (2.0)	5 (5.2)	3 (3.1)
Hyperthyroidism	3 (2.0)	0	7 (7.3)	1 (1.0)
Amylase increased	2 (1.4)	0	6 (6.3)	4 (4.2)
Vomiting	2 (1.4)	0	8 (8.3)	0
Pyrexia	2 (1.4)	0	5 (5.2)	0
Colitis	0	0	9 (9.4)	4 (4.2)

Data are based on a database lock of November 6, 2017, and include events reported from the time of the first dose of study drug to 30 days after the last dose. Events with an outcome of death are reported according to the grade experienced at presentation.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

in patients with NSCLC (nivolumab, 3 mg/kg every 2 weeks; ipilimumab, 1 mg/kg every 6 weeks)[15-17]; however, the safety profiles of both monotherapy and combination treatment were in accordance with those observed in other tumor types,[2] and no new safety signals were identified.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.10.004.

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