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**Third-Line Nivolumab Monotherapy in Recurrent Small Cell Lung Cancer:
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ABBREVIATIONS

1L = first-line

2L = second-line

3L+ = third- or later line

AE = adverse event

BICR = blinded independent central review

CI = confidence interval

DOR = duration of response

ECOG PS = Eastern Cooperative Oncology Group performance status

FDA = US Food and Drug Administration

NSCLC = non-small cell lung cancer

ORR = objective response rate

OS = overall survival

PD-1 = programmed death-1

PD-L1 = programmed death ligand 1

SCLC = small cell lung cancer

TMB = tumor mutational burden

TRAE = treatment-related adverse event

ABSTRACT

Introduction: For patients with recurrent small cell lung cancer (SCLC), topotecan remains the only FDA-approved or EMA-approved second-line treatment, and outcomes are poor. CheckMate 032 is a phase 1/2, multicenter, open-label study of nivolumab or nivolumab plus ipilimumab in SCLC or other advanced/metastatic solid tumors previously treated with ≥ 1 platinum-based chemotherapies. We report results of third- or later-line (3L+) nivolumab monotherapy treatment in SCLC.

Methods: In this analysis, patients with limited-stage or extensive-stage SCLC and disease progression after ≥ 2 chemotherapy regimens received nivolumab monotherapy 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The primary end point was objective response rate (ORR). Secondary end points included duration of response (DOR), progression-free survival, overall survival, and safety.

Results: Between December 4, 2013 and November 30, 2016, 109 patients initiated 3L+ nivolumab monotherapy. At a median follow-up of 28.3 months (from first dose to database lock), ORR was 11.9% (95% confidence interval: 6.5–19.5) with a median DOR of 17.9 months (range, 3.0 to 42.1). At 6 months, 17.2% of patients were progression-free. The 12-month and 18-month overall survival rates were 28.3% and 20.0%, respectively. Grade 3–4 treatment-related adverse events (TRAEs) occurred in 11.9% of patients. Three patients (2.8%) discontinued due to TRAEs.

Conclusions: Nivolumab monotherapy provided durable responses and was well tolerated as a 3L+ treatment for recurrent SCLC. These results suggest that nivolumab monotherapy is an effective 3L+ treatment for this patient population.

Keywords: Small cell lung cancer; Third-line; Nivolumab; PD-1 inhibitor; Immunotherapy

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Introduction

Small cell lung cancer (SCLC) is an aggressive disease with no treatment options that produce durable responses.¹⁻³ Current first-line (1L) treatments include platinum-based chemotherapy, which have good initial response rates (60% to 80% for extensive-stage disease); however, nearly all patients relapse shortly after treatment and median survival is only 1 to 2 years from the time of diagnosis.^{2,4} The only second-line (2L) therapy for SCLC is topotecan, which was initially approved as an intravenous formulation in 1998 and as an oral formulation in 2007. The median duration of response (DOR) with intravenous topotecan is 3.3 months,⁵ and treatment is characterized by high rates of grade 4 neutropenia (intravenous, 70%; oral, 32%), grade 4 thrombocytopenia (intravenous, 29%; oral, 6%), and grade 3–4 anemia (intravenous, 42%; oral, 25%).^{6,7}

Nivolumab is a fully human immunoglobulin G4 programmed death (PD)–1 immune checkpoint inhibitor antibody approved for the treatment of various cancer types, including previously treated non-small cell lung cancer (NSCLC).⁸ Overall survival (OS) was significantly prolonged with nivolumab versus docetaxel in a pooled analysis of patients with previously treated advanced NSCLC from the phase 3 CheckMate 017 and 057 trials (pooled hazard ratio = 0.70 [95% confidence interval (CI): 0.61–0.81]).⁹ In a long-term analysis of patients with previously treated advanced NSCLC from the phase 1 CA209-003 study, the estimated 5-year OS rate was 16% with nivolumab monotherapy.¹⁰ On August 16, 2018, nivolumab monotherapy received approval by the US Food and Drug Administration (FDA) for the treatment of patients with metastatic

SCLC with progression after platinum-based chemotherapy and at least one other line of therapy based on results presented in this manuscript.

CheckMate 032 (ClinicalTrials.gov number, NCT01928394) is a multicenter, open-label, phase 1/2 trial evaluating nivolumab alone or in combination with ipilimumab in previously treated advanced or metastatic solid tumors. In an interim analysis of this study, a manageable safety profile and durable responses were observed with nivolumab monotherapy in a nonrandomized cohort of patients with SCLC and ≥ 1 prior platinum-based chemotherapy regimens.¹¹ Here we report the efficacy and safety of third- or later-line (3L+) nivolumab monotherapy from pooled nonrandomized and randomized cohorts of patients with recurrent SCLC from CheckMate 032.

Patients and Methods

Study Design and Treatment

Patients enrolled in CheckMate 032 were assigned to separate cohorts according to tumor type. Eligibility criteria for the SCLC cohort of CheckMate 032 included ≥ 18 years of age, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, histologically or cytologically confirmed limited-stage or extensive-stage SCLC, and previous treatment with one or more platinum-based chemotherapy regimens. The current analysis includes patients with disease progression after two or more prior chemotherapy regimens. Patients were eligible regardless of platinum sensitivity or tumor programmed death ligand 1 (PD-L1) expression. Further eligibility criteria and trial details have been previously reported.¹¹

Patients with SCLC were initially enrolled as part of a nonrandomized cohort (Supplementary Fig. 1), the design of which has been previously described.¹¹ A subsequent randomized cohort was added to confirm clinical activity observed in the initial phase. The analysis here reports pooled results from the monotherapy arms of the nonrandomized and randomized cohorts. In both cohorts, nivolumab monotherapy 3 mg/kg was administered every 2 weeks until disease progression or unacceptable toxicity. Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg was also evaluated in both cohorts, the results of which will be reported separately. As previously reported, nivolumab 1 mg/kg plus ipilimumab 1 mg/kg and nivolumab 3 mg/kg plus ipilimumab 1 mg/kg doses were also assessed in the nonrandomized dose-escalation cohort.¹¹

The primary end point of this study was objective response rate (ORR) by blinded independent central review (BICR) assessment per Response Evaluation Criteria in Solid Tumors version 1.1.¹² DOR by BICR, progression-free survival by BICR, OS, and safety were also evaluated as secondary end points. Tumor assessments were conducted at baseline, every 6 weeks for the first 24 weeks, and every 12 weeks thereafter until disease progression or treatment discontinuation. Survival was monitored every 3 months after treatment discontinuation. Safety was evaluated throughout the study, and adverse events (AEs) were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0.

Tumor PD-L1 expression was assessed retrospectively in pretreatment (archival or fresh) tumor biopsy specimens with the use of a validated, automated immunohistochemical assay (Dako North America, Carpinteria, CA) using a rabbit anti-human PD-L1 antibody (clone 28-8; Epitomics Inc, Burlingame, CA).¹³ Tumor PD-L1

expression was categorized as positive when staining of tumor-cell membranes (at any intensity) was observed at prespecified expression levels ($\geq 1\%$ of tumor cells in a section that included ≥ 100 evaluable tumor cells).

The study protocol was approved by an institutional review board or independent ethics committee at each participating center. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonisation. Written informed consent was collected from all patients prior to enrollment. BMS policy on data sharing may be found at <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>.

Statistical Analysis

Data included in this analysis were pooled from the nonrandomized and randomized cohorts. Analyses for efficacy were conducted as described previously.¹¹ The safety profile of nivolumab was assessed in all treated patients through summaries and by-subject listings of deaths, serious AEs, AEs leading to discontinuation, overall AEs, and select AEs. The database lock for this analysis was November 6, 2017.

Results

Patients and Treatment

In the pooled SCLC cohort of CheckMate 032, 109 patients (nonrandomized cohort, $n = 59$; randomized cohort, $n = 50$) initiated 3L+ nivolumab monotherapy between December 4, 2013 and November 30, 2016. Baseline patient characteristics are presented in Table 1. Briefly, median patient age was 64 years, 92.7% of patients

were current or former smokers, and 56.0% were male. Approximately 17% of patients with quantifiable PD-L1 had $\geq 1\%$ tumor PD-L1 expression. The majority (71.6%) of patients were treated with two prior systemic treatment regimens; 22.9% were treated with three, and 5.5% with four or more prior systemic regimens. Prior platinum-based therapies included carboplatin in 67.0% of patients and cisplatin in 56.9% of patients. Nearly two-thirds of patients (65.1%) had platinum-sensitive SCLC (defined as progression-free ≥ 90 days after completion of platinum-based chemotherapy) and one-third (33.9%) had platinum-resistant disease.

At a minimum follow-up of 11.9 months (median time from first dose to database lock, 28.3 months), 8 patients (7.3%) remained on 3L+ nivolumab monotherapy. Among patients who did not continue nivolumab monotherapy, the most common reason for treatment discontinuation was disease progression (74.3%; Supplementary Table 1). The median duration of nivolumab monotherapy was 1.2 months (range, 0.0 to 44.2+; + symbol indicates a censored value).

Efficacy

In 109 patients treated with 3L+ nivolumab monotherapy, confirmed ORR was 11.9% (95% CI: 6.5–19.5; Table 2). The median DOR was 17.9 months (95% CI: 7.9–42.0; range, 3.0 to 42.1; Fig. 1); DOR was at least 12 months in 61.5% of patients with an objective response (Table 2). Response rates were similar across most patient subgroups, including patients with $< 1\%$ and $\geq 1\%$ tumor PD-L1 expression, with the exception of ECOG PS where ORR was higher in patients with an ECOG PS of 0 versus 1 (21.9% versus 6.6%; Supplementary Table 2).

The median progression-free survival in patients treated with 3L+ nivolumab monotherapy was 1.4 months (95% CI: 1.3–1.6), and 17.2% (95% CI: 10.7–25.1) of patients were progression-free at 6 months according to Kaplan-Meier estimates (Fig. 2). The median OS was 5.6 months (95% CI: 3.1–6.8), with a 12-month OS rate of 28.3% (95% CI: 20.0–37.2) and an 18-month OS rate of 20.0% (95% CI: 12.7–28.6; Fig. 3).

Safety

Any grade and grade 3–4 treatment-related adverse events (TRAEs) with 3L+ nivolumab monotherapy were reported in 55.0% and 11.9% of patients, respectively (Table 3). Three percent of patients discontinued treatment due to TRAEs, all of which were grade 3–4. Most select TRAEs (defined as AEs of potential immunologic causes) were grade 1–2 (Supplementary Table 3). The most common select TRAEs of any grade were skin reactions (21.1%); the most frequent 3–4 select TRAEs were pulmonary events (1.8%; n = 2, both pneumonitis). One treatment-related neurologic AE (grade 3–4 encephalitis) was reported. One treatment-related death due to pneumonitis was noted.

Discussion

In this analysis from CheckMate 032, nivolumab monotherapy resulted in an objective response by BICR in 11.9% of patients with recurrent limited-stage or extensive-stage SCLC previously treated with two or more chemotherapy regimens. Patients whose tumors were platinum refractory to 1L therapy were included, and there was no selection by biomarker such as tumor PD-L1 expression. Among patients who

responded to nivolumab, 61.5% experienced durable DORs lasting at least 1 year (median DOR, 17.9 months). Response rates were similar across most patient subgroups, with the exception of ECOG PS; ORR was higher in patients with an ECOG PS of 0 (21.9%) versus 1 (6.6%). Overall, nivolumab monotherapy was well tolerated, with a low (2.8%) discontinuation rate due to TRAEs. These results supported the recent FDA approval of nivolumab for the treatment of patients with metastatic SCLC that progressed after platinum-based chemotherapy and at least one other line of therapy.

Patients who have received two or more previous lines of therapy for SCLC are often symptomatic from progression of cancer, side effects of previous therapy, and comorbidities. Choices for such patients in the past have included best supportive care with hospice, additional cytotoxic chemotherapy, and clinical trials. The current analysis addresses a need for data in patients with SCLC who have progressed following multiple lines of therapy. Reports have indicated that approximately 10% to 20% of patients who receive 1L chemotherapy will subsequently receive therapy in the 3L setting.¹⁴⁻¹⁶ The current National Comprehensive Cancer Network guidelines do not provide a specific recommendation for 3L+ treatment, but recommend enrollment in clinical trials as the preferred option.³ An area of unmet medical need in the 3L+ treatment of SCLC is effective therapy that does not add to the side effects of cytotoxic chemotherapy. Nivolumab is listed among several other systemic therapy options in the National Comprehensive Cancer Network guidelines, consistent with the recent FDA approval of nivolumab for the 3L+ treatment of metastatic SCLC.

Data supporting 3L+ therapies in patients with SCLC are limited to reports of real-world evidence. An international real-world, retrospective analysis evaluating 3L chemotherapy treatment in patients with SCLC (N = 120) reported a median OS of 4.7 months and response rate of 18%; of note, DOR was not reported in this study.¹⁷ However in that study, responses were investigator determined, and the population mostly included patients with platinum-sensitive disease who received two different platinum-based chemotherapy combination regimens. Therefore, these data cannot be directly compared with our analysis. In a recent analysis of a US-based, real-world patient cohort matched to the CheckMate 032 population and who received 3L therapy for SCLC (n = 92), the 1-year OS rate was 11% (poster to be presented at the World Conference on Lung Cancer on September 23–26, 2018 in Toronto, Canada [abstract #13791]). Patients in this cohort did not receive 3L immunotherapy treatment, highlighting the benefit of nivolumab monotherapy reported in the present CheckMate 032 analysis (1-year OS rate, 28.3%). The patients evaluated in this study of nivolumab were largely representative of the previously treated SCLC population and, to our knowledge, represent the largest cohort of patients with recurrent SCLC treated with a 3L+ immune checkpoint inhibitor.

Although results from several studies in patients with recurrent SCLC have recently been presented, few have reported data specifically in 3L populations. A subgroup analysis of the phase 2 TRINITY study in the 3L+ population reported an independent review committee–assessed ORR of 16% (28/177) in biomarker-selected patients treated with 3L rovalpituzumab tesirine, an antibody-drug conjugate that targets Delta Like Canonical Notch Ligand 3 (DLL3).¹⁸ The independent review committee–

assessed DOR in this study was 4.1 months (95% CI: 3.0–4.2). Recently reported phase 1/2 studies of immuno-oncology agents included biomarker-unselected patients treated with at least one prior line of therapy, with ORRs ranging from 9.5% to 18.7% and landmark 1-year OS rates of 28% to 43%.^{11,19-21}

Ideally, identifying subsets of patients more likely to benefit from treatment with nivolumab monotherapy remains an important research goal. Tumor PD-L1 expression is a biomarker for response to PD-1 inhibitors in patients with NSCLC²²; however, as measured using the validated Dako PD-L1 IHC 28-8 pharmDx assay, it did not appear to predict response to nivolumab in the present 3L+ analysis of CheckMate 032, or in an interim analysis of the 2L+ nonrandomized cohort of this study.¹¹ Emerging exploratory data from the KEYNOTE-158 study, which uses the combined positive score assay (includes tumor cells and intercalating immune cells that stain positive for PD-L1), suggests a potential role for PD-L1 expression in selecting patients with SCLC who may respond to PD-1 inhibitors.²⁰

Tumor mutational burden (TMB) is also emerging as an independent biomarker of response to immune checkpoint inhibitors in various cancer types, including SCLC, NSCLC, bladder cancer, and melanoma.²³⁻³³ In a separate analysis of the pooled nivolumab monotherapy cohort in CheckMate 032, ORR was 21.3% in patients with high TMB (≥ 248 mutations by whole exome sequencing) versus 4.8% in those with low TMB (0 to < 143 mutations).²⁵ Future prospective evaluations of nivolumab monotherapy in a TMB-selected population with SCLC may help identify patients more likely to respond.

Patients with SCLC who have progressed on multiple lines of treatment have few therapeutic options in the 3L and beyond. Best supportive care, often including hospice, is the best choice for some patients in this setting. Clinical trials remain an important option in previously treated SCLC. Here we show that clinically meaningful results are achievable with nivolumab monotherapy in a population with biomarker-unselected SCLC and ECOG PS ≤ 1 , including patients with platinum-refractory disease. Responses to nivolumab are durable in the minority of patients who respond, with a tolerable safety profile. For patients who have received multiple lines of therapy for metastatic SCLC, nivolumab may provide an additional treatment option. Furthermore, these data warrant further investigation of immuno-oncology approaches in SCLC. Additional analyses of the randomized SCLC cohort of CheckMate 032, including patients treated with the combination of nivolumab plus ipilimumab, are underway and will be published separately. Phase 3 studies evaluating nivolumab alone and in combination with ipilimumab for SCLC as maintenance treatment after induction therapy (ClinicalTrials.gov number, NCT02538666) and nivolumab monotherapy for SCLC in the 2L setting (ClinicalTrials.gov number, NCT02481830) are ongoing.

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FIGURE LEGENDS

Figure 1. DOR by blinded independent central review with 3L+ nivolumab monotherapy. 3L+, third- or later line; CI, confidence interval; DOR, duration of response.

Figure 2. PFS by blinded independent central review with 3L+ nivolumab monotherapy. 3L+, third- or later line; CI, confidence interval; PFS, progression-free survival.

Figure 3. OS with 3L+ nivolumab monotherapy. 3L+, third- or later line; CI, confidence interval; OS, overall survival.

TABLES

Table 1. Baseline Characteristics in Patients Treated With 3L+ Nivolumab Monotherapy

	3L+ Nivolumab (n = 109)
Median (range) age, y	64.0 (45–81)
≥75 years, n (%)	7 (6.4)
Male, n (%)	61 (56.0)
Race, n (%)	
White	102 (93.6)
Black/African American	4 (3.7)
Other	3 (2.8)
Prior systemic treatment regimens, n (%)	
2	78 (71.6)
3	25 (22.9)
>3	6 (5.5)
First-line platinum-treated patients, n (%)	
Platinum-sensitive ^a	71 (65.1)
Platinum-resistant ^b	37 (33.9)
Unknown	1 (0.9)
Smoking status, n (%)	
Current/former smoker	101 (92.7)
Never smoker	8 (7.3)
ECOG PS, n (%)	
0	32 (29.4)

1	76 (69.7)
2 ^c	1 (0.9)
Tumor PD-L1 expression, n (%)	
<1%	65 (59.6)
≥1%	13 (11.9)
Not quantifiable ^d	31 (28.4)

^aProgression-free ≥90 days after completion of platinum-based chemotherapy.

^bProgression-free <90 days after completion of platinum-based chemotherapy.

^cPatients with an ECOG PS score ≥2 were not eligible for inclusion in this study. The patient who had an ECOG PS of 2 at baseline had a PS of 1 at screening and a PS of 2 at the first dosing date 15 days later.

^dNot evaluable, indeterminate, or missing.

3L+, third- or later line; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1.

Table 2. ORRs With 3L+ Nivolumab Monotherapy

	3L+ Nivolumab (n = 109)
ORR by BICR ^a	
No. of patients	13
% of patients (95% CI)	11.9 (6.5–19.5)
Best overall response, n (%)	
Complete response	1 (0.9)
Partial response	12 (11.0)
Stable disease	25 (22.9)
Progressive disease	56 (51.4)
Unable to determine	14 (12.8)
Not reported	1 (0.9)
Median time to response, months	1.6
Duration of response	
≥6 months, n (%)	10 (76.9)
≥12 months, n (%)	8 (61.5)
Median (95% CI), months ^b	17.9 (7.9–42.0)
Range, months	3.0–42.1

^aPer Response Evaluation Criteria in Solid Tumors v1.1.

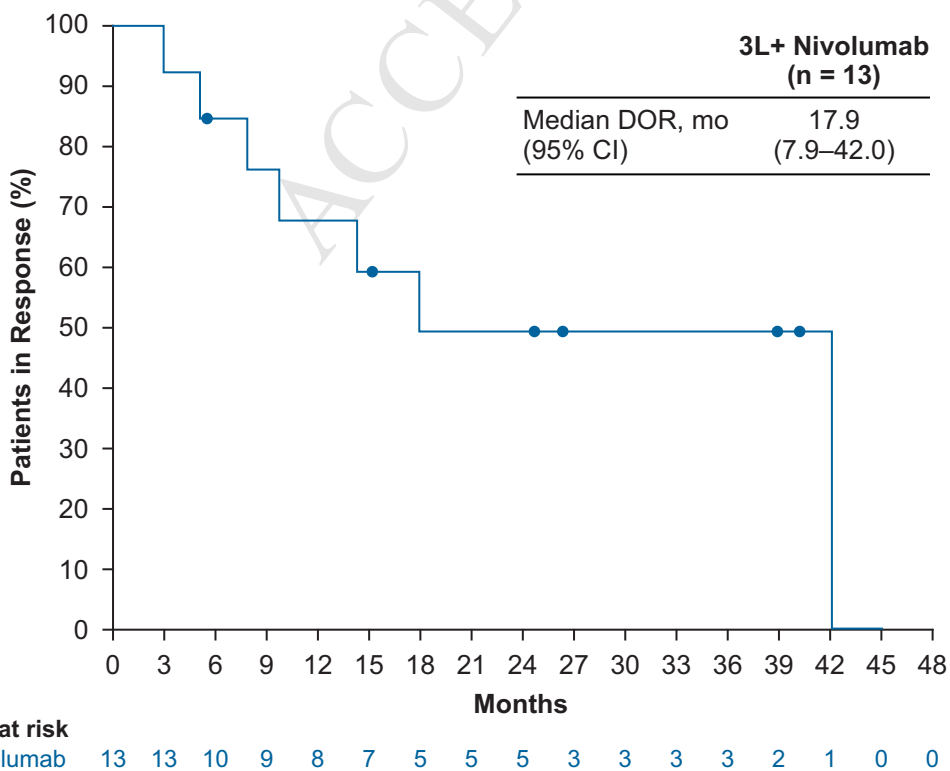
^bComputed using Kaplan-Meier method.

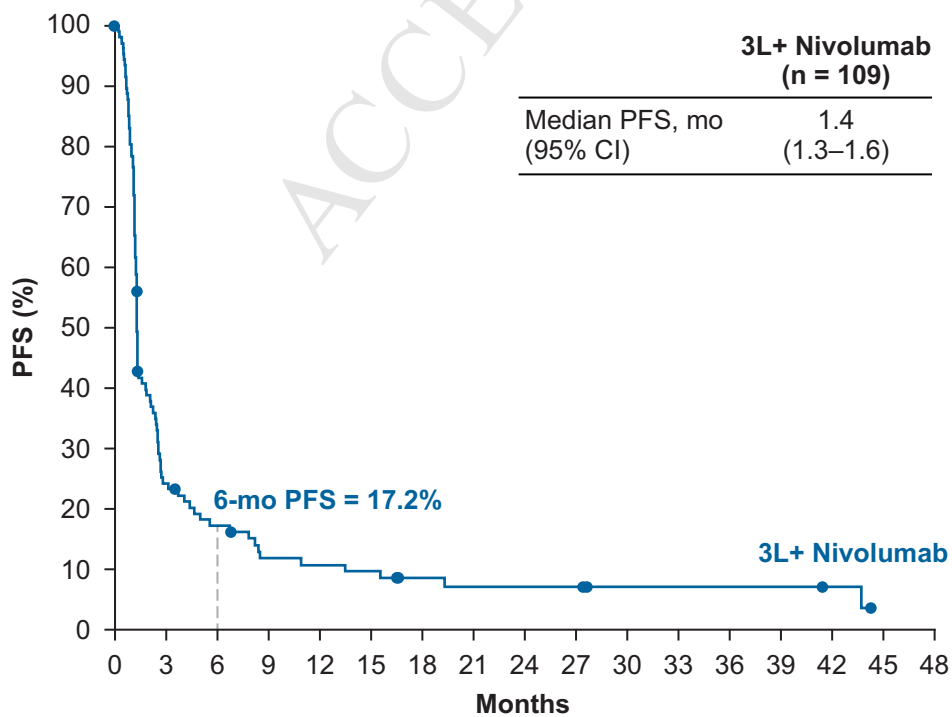
3L+, third- or later line; BICR, blinded independent central review; CI, confidence interval; ORR, objective response rate.

Table 3. Treatment-Related Adverse Events

Event, n (%)	3L+ Nivolumab (n = 109)	
	Any Grade	Grade 3–4
Any event	60 (55.0)	13 (11.9)
Any serious event	9 (8.3)	8 (7.3)
Any event leading to discontinuation	3 (2.8)	3 (2.8)
Most frequent events ($\geq 5\%$)		
Pruritus	14 (12.8)	0
Fatigue	11 (10.1)	1 (0.9)
Nausea	8 (7.3)	0
Rash	7 (6.4)	1 (0.9)
Diarrhea	7 (6.4)	0
Decreased appetite	6 (5.5)	1 (0.9)

Data are based on a November 6, 2017 database lock. Safety analysis included all patients who received at least one dose of study drug. Includes events reported from the time of the first dose of study drug to 30 days after the last dose.





No. at risk

Nivolumab 109 25 17 11 10 9 6 5 5 5 3 3 3 3 2 0 0

