Efficacy of Nivolumab and Pembrolizumab in Patients With Advanced Non–Small-Cell Lung Cancer Needing Treatment Interruption Because of Adverse Events: A Retrospective Multicenter Analysis

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Abstract

Nivolumab and pembrolizumab can cause immune-related adverse events (irAE). In this retrospective chart review of advanced non–small-cell lung cancer patients receiving programmed death 1 antibodies in British Columbia, Canada, treatment interruption due to irAE was associated with a lower median overall survival (OS) than those treated continuously. Development of colitis in nivolumab-treated patients was associated with shorter OS than for patients who did not develop colitis.

Introduction: The programmed death 1 antibodies (PD-1 Ab) nivolumab and pembrolizumab improve overall survival (OS) in advanced non–small-cell lung cancer (NSCLC). We evaluated the correlation between immune-related adverse events (irAE) and treatment interruption due to irAE on clinical efficacy of PD-1 Ab in advanced NSCLC. **Patients and Methods:** Advanced NSCLC patients treated with PD-1 Ab between June 2015 to November 2017 at BC Cancer were identified. Demographic, tumor, treatment details, and frequency and grade (Common Terminology Criteria for Adverse Events, version 4.0) of irAE were abstracted from chart review. Kaplan-Meier curves of OS from initiation of PD-1 Ab were generated. Multivariable analysis with 6- and 12-week landmark analysis was performed by Cox proportional hazard regression models. **Results:** In a cohort of 271 patients, irAEs were observed in 116 patients (42.8%). Nivolumab recipients developing colitis had lower OS compared to those who did not at the 6-week landmark ($P = .010$) and 12-week landmark ($P = .072$). For the entire cohort, 56 patients (20.7%) needed treatment interruption because of an irAE. Treatment interruption correlated with lower OS at the 6-week landmark ($P = .005$) and 12-week landmark ($P = .008$). Six-week landmark multivariable analysis identified Charlson Comorbidity Index score of 3 or higher, Eastern Cooperative Oncology Group Performance Status of 2 or higher, presence of liver metastases, and irAE greater than grade 2 versus no irAE to be associated with decreased OS (each $P < .05$). **Conclusion:** Treatment interruption due to irAE was associated with a lower median OS compared to continuous PD-1 Ab therapy. Shorter OS seen with severe irAE might reflect the need for improved physician education in irAE treatment algorithms.

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Introduction

Expression of inhibitory receptors on tumor-infiltrating T cells such as programmed death protein 1 (PD-1) is one mechanism contributing to immune tolerance in the tumor environment.[1] Pembrolizumab, a humanized immunoglobulin G4 kappa antagonist antibody to PD-1, increases overall survival (OS) of patients

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with advanced non–small-cell lung cancer (NSCLC) in the first- and second-line settings compared to chemotherapy with palliative intent.[2,3] Nivolumab, a fully human immunoglobulin G4 kappa monoclonal antagonist antibody to PD-1, prolongs OS compared to docetaxel for incurable NSCLC in the second-line setting.[4,5]

PD-1 antibodies can result in unique adverse events termed immune-related adverse events (irAE); they are believed to be a consequence of uninhibited immune response, causing primarily T-cell–mediated autoimmunity.[6] The most common irAEs associated with PD-1 antibodies involve the skin, colon, lungs, and thyroid.[2-5] irAEs are usually low grade, but about 10% are grade 3 or 4, requiring treatment with corticosteroids or immune-modulating agents.[7]

Patients treated in everyday clinical practice (ie, those with poor Eastern Cooperative Oncology performance status [ECOG PS] or multiple medical comorbidities) tend to be underrepresented in randomized clinical trials[8,9]; these poor-prognosis patients might experience more adverse events or treatment interruptions than those enrolled onto pivotal PD-1 antibody trials. While efficacy outcomes among patients requiring treatment discontinuation due to irAE have been found to be similar to those treated continuously with immunotherapy in advanced melanoma, a parallel result in NSCLC is less clear.[10]

Development of irAE might signal that an immune reaction has been activated.[11-14] Specifically, development of pneumonitis, dermatitis, and thyroid abnormalities in nivolumab recipients with advanced NSCLC have been associated with improved OS.[13-15]

In British Columbia, Canada, pembrolizumab is available as a first-line treatment for patients with incurable NSCLC and programmed death ligand 1 (PD-L1) tumor proportion score (TPS) over 50% and as a second-line treatment if PD-L1 TPS exceeds 1%. Nivolumab can be provided after disease progression on platinum-based doublet therapy, regardless of PD-L1 TPS.

We evaluated for a potential association between irAE in pembrolizumab- or nivolumab-treated patients with advanced NSCLC and OS using landmark analysis. We also investigated the effect of treatment interruption (either delay in treatment or cessation of immunotherapy) due to irAE on clinical efficacy.

Patients and Methods

We identified patients with advanced NSCLC (stage IV, 7th edition, International Union Against Cancer tumor, node, metastasis classification system, or recurrent nonresectable disease not amenable to curative-intent radiotherapy) treated with nivolumab or pembrolizumab at 1 of 6 BC Cancer centers between June 2015 to October 2017. Retrospective chart review was conducted from initial referral to BC Cancer until March 2018 by 6 medical oncologists who specialized in lung cancer. The first author subsequently reviewed all charts to ensure consistency. The study was conducted in accordance with the principles of good clinical practice and approval from the institutional review board.

Demographic and Tumor Characteristics

The following clinical characteristics at the start of PD-1 inhibitor treatment were abstracted: age, gender, ECOG PS (if not stated explicitly in the chart, the reviewing oncologist made an estimate on the basis of the clinical narrative), smoking status, and location of metastases. Charlson comorbidity index (CCI) score was tabulated by the abstractor on the basis of the presence or absence of 19 medical conditions (advanced NSCLC was not included as a "solid metastatic tumor") listed in the initial medical oncology consultation note.[16] Tumor-specific factors included histologic subtype, presence of epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) rearrangement, and PD-L1 TPS analyzed by immunohistochemical staining using PD-L1 IHC 22c3 pharmDx antibody, clone 22C3; (Dako North America, Carpinteria, CA). Of note, *EGFR* mutation and *ALK* rearrangement testing were conducted in a standard manner on nonsquamous tumors at a central laboratory. Routine testing of PD-L1 TPS for advanced NSCLC began in January 2017.

Treatment Characteristics

Receipt of radiotherapy preceding PD-1 antibody treatment, adjuvant chemotherapy, and number of previous lines of palliative-intent chemotherapy were recorded. PD-1 inhibitors were administered according to standard dosing: nivolumab 3 mg/kg body weight every 2 weeks and pembrolizumab 2 mg/kg body weight every 3 weeks. Presence of irAE was based on assessment by treating physician; the abstractor utilized the Common Terminology Criteria for Adverse Events, version 4.0, to grade the irAE. BC Cancer medical oncologists utilized protocol-driven algorithms to treat irAE and help them with decision making to stop PD-1 inhibitors due to irAE.[17,18] Treatment interruption was defined as including either delay or cessation of PD-1 antibody therapy due to an irAE.

Survival Assessment

OS was calculated from the time of initiation of nivolumab or pembrolizumab until death from any cause or last follow-up. Progression-free survival (PFS) was calculated as the time from initiation of PD-1 antibody until tumor progression as determined by the treating physician, death from any cause, or last follow-up, whichever occurred first.

Statistical Analysis

Clinical and disease characteristics were summarized as medians and ranges for continuous variables and as frequencies and percentages for categorical variables. The Fisher exact test was used to compare irAE characteristics between groups. Kaplan-Meier OS curves from initiation of PD-1 antibody were generated and groups compared by the log-rank test. Univariable and multivariable Cox proportional hazard models were fitted to determine associations between demographic and clinical characteristics and survival outcomes.

Landmark analysis was used to minimize lead-time bias associated with time-dependent factors.[12,19] A landmark analysis includes patients in the risk set at a set time point, excluding patients who died or who were censored before this time point. Six-week landmark analysis included 254 patients (214 nivolumab and 40 pembrolizumab), and outcomes for patients who developed a given irAE within 6 weeks of initiation of PD-1 antibodies were compared with those who did not. A similar 12-week landmark analysis was also performed and included 224 patients (185 who received nivolumab and 29 pembrolizumab). This method was used to obtain unbiased estimates because the irAE groups were determined during study

follow-up rather than at time 0—the time of initiation of PD-1 antibody treatment.

All *P* values were based on 2-sided hypotheses tests, and *P* values less than .05 were considered statistically significant. Statistical analyses were performed by R 3.2.3 and the R package "survival" 2.40.1.[20,21]

Results

Patients

A total of 271 patients with advanced NSCLC met the eligibility criteria; there were 230 nivolumab-treated and 41 pembrolizumab-treated patients. The baseline clinical characteristics for the study cohort at initiation of PD-1 antibody are summarized in Table 1. Of note, 84 patients (31.0%) were ≥ 70 years old, 84 patients (31.0%) had ECOG PS ≥ 2, 182 patients (67%) had CCI ≥ 3, 36 patients (13.3%) had brain metastases, and 33 patients (12.2%) had liver metastasis. One patient received pembrolizumab as part of a clinical trial. Regarding tumor characteristics, 67 patients (24.7%) had squamous-cell tumors, 16 (5.9%) had an *EGFR* mutation, and 3 (1.1%) had an *ALK* rearrangement. PD-L1 staining of < 1%, 1%-49%, > 50%, and unknown for nivolumab-treated patients was 11.7%, 9.1%, 10.9%, and 68.3%, and among pembrolizumab recipients was 0, 12.2%, 82.9%, and 4.9%, respectively. One hundred sixty-five (71.7%) of 230 nivolumab-treated patients received the drug in the second therapy line, while 17 (41.5%) of 41 pembrolizumab-treated patients received the drug in the first therapy line.

Treatment

With a median (range) follow-up from initiation of PD-1 antibodies of 8.1 (0.1-33.9) months, median treatment duration of nivolumab was 3.7 (0.5-30.0) months and for pembrolizumab was 5.5 (0.70-23.5) months. A median (range) of 8 (1-65) doses of nivolumab and 8 (1-34) doses of pembrolizumab were delivered. At last follow-up, 55 (23.9%) of 230 nivolumab-treated patients and 14 (34.1%) of 41 pembrolizumab-treated patients were still receiving PD-1 antibodies.

Efficacy in All Patients

At last follow-up, 143 (62.2%) of 230 nivolumab recipients and 19 (46.3%) of 41 pembrolizumab recipients had died. Among nivolumab recipients, median PFS and OS were 5.7 months (95% confidence interval [CI], 4.1-8.8) and 9.2 months (95% CI, 7.8-12.4), respectively (Figure 1). In the nivolumab group, median OS for squamous tumors was 12.9 months (95% CI 5.6-not reached [NR]) and for nonsquamous tumors was 8.5 months (95% CI, 7.1-10.7). The PFS and median OS for pembrolizumab recipients were 13.5 months (95% CI, 8.2-NR) and 13.5 months (95% CI, 10.6-NR), respectively.

Utilizing 6-week landmark multivariate Cox proportional hazard regression analysis, CCI ≥ 3 ($P < .001$), ECOG PS ≥ 2 ($P < .001$), presence of liver metastases ($P = .017$), and irAE > grade 2 versus no irAE ($P = .036$) were significantly associated with decreased OS (Table 2). Not significant were age, sex, smoking status, histology, brain metastases, *EGFR* mutation status, and type of PD-1 therapy. At 12-week landmark analysis, CCI ≥ 3 ($P < .001$) and ECOG PS ≥ 2 ($P < .001$) remained correlated with shorter OS.

Table 1 Baseline Demographic and Clinical Characteristics of Patients Treated With PD-1 Ab

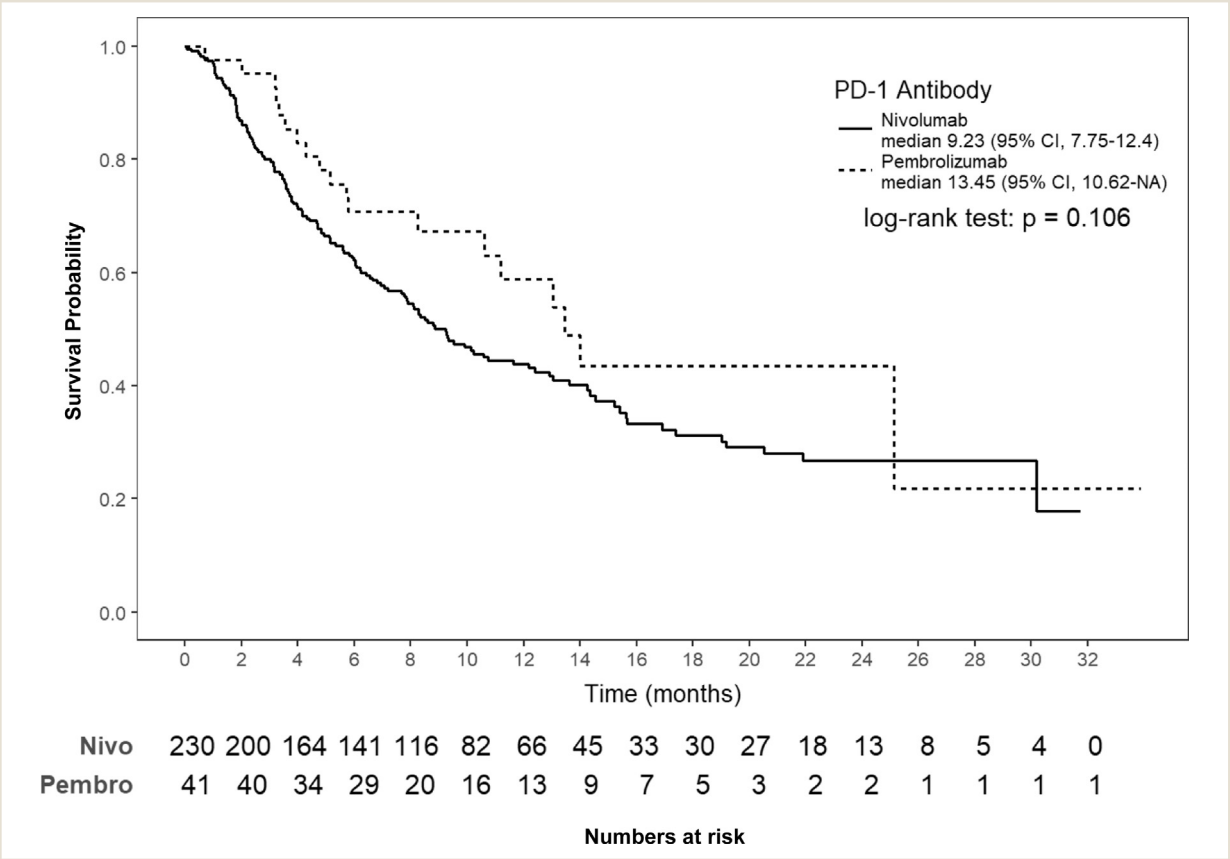
Characteristic	Nivolumab (N = 230)	Pembrolizumab (N = 41)
Age (y)	64 (39-82)	68 (50-81)
Sex		
Male	116 (50.4)	21 (51.2)
Female	114 (49.6)	20 (48.8)
ECOG PS at Initiation of PD-1 Ab		
0/1	159 (69.1)	28 (68.2)
≥2	71 (30.9)	13 (31.7)
Histologic Subtype		
Squamous	59 (25.7)	8 (19.5)
Nonsquamous	171 (74.3)	33 (80.5)
Smoking Status		
Nonsmoker	32 (13.9)	2 (4.9)
Current smoker	76 (33.0)	17 (41.5)
Former smoker	122 (53.0)	22 (53.7)
Tumor Molecular Aberration		
EGFR mutation	13 (5.7)	3 (7.3)
ALK rearrangement	3 (1.3)	0 (0.0)
PD-L1 Staining		
<1%	27 (11.7)	0 (0.0)
1%-49%	21 (9.1)	5 (12.2)
≥50%	25 (10.9)	34 (82.9)
Unknown	157 (68.3)	2 (4.9)
Brain metastases	30 (13.0)	6 (14.6)
Liver metastases	28 (12.2)	5 (12.2)
CCI score	6.0 (0.0-12.0)	4.0 (0.0-11.0)
Stage IV disease at diagnosis	142 (61.7)	30 (73.2)
Prior adjuvant chemotherapy	17 (7.4)	4 (9.8)
Prior chest RT	125 (54.3)	28 (68.3)
Treatment Line		
First	4 (1.7)	17 (41.5)
Second	165 (71.7)	19 (46.3)
Third or higher	61 (26.6)	5 (12.2)
No. of PD-1 treatments	8 (1-65)	8 (1-34)

Data are presented as n (%) or median (range).
Abbreviations: ALK = anaplastic lymphoma kinase; CCI = Charlson comorbidity index; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; PD-1 Ab = programmed death 1 antibody; PD-L1 = programmed death ligand 1; RT = radiotherapy.

Safety

A total of 116 patients (42.8%) in the study cohort developed an irAE, with 10.0% in the nivolumab group and 4.9% in the pembrolizumab group experiencing an irAE grade of 3 or higher (Table 3). In the whole cohort, the most common irAEs were dermatitis (12.9%), hypothyroidism (11.8%), colitis (6.6%), and pneumonitis (6.3%). The incidence of pneumonitis (14.6% vs. 4.8%, $P = .028$) and arthralgias (12.2% vs. 3.5%, $P = .032$) were greater in the pembrolizumab than the nivolumab group. Three treatment-related deaths (all in nivolumab recipients) were attributed to pneumonitis, hepatitis, and colitis. Systemic corticosteroids

Figure 1 Kaplan-Meier Curves of Overall Survival From Initiation of PD-1 Antibodies



Abbreviation: PD-1 = programmed cell death 1.

were administered to 25.2% of nivolumab-treated patients and 19.5% of pembrolizumab-treated patients ($P = .557$). Fifteen patients (5.5%) required overnight hospitalization, and 1 patient (0.4%) needed admission to an intensive care unit for immune-related complications.

In the entire cohort, 24 patients (8.9%) required dose delay due to irAE, and 32 patients (11.8%) permanently discontinued treatment. Dose delay due to irAE occurred in 20 patients in the nivolumab group and 4 patients in the pembrolizumab group; discontinuation of PD-1 antibody due to irAE was required in 28 nivolumab-treated and 4 pembrolizumab-treated patients. There was no statistically significant difference in age, sex, ECOG PS, smoking status, histology, *EGFR/ALK* status, presence of brain metastases, presence of liver metastases, CCI score, treatment line of PD-1 antibody, total number of cycles delivered between patients receiving treatment continuously, and those requiring an interruption due to irAE (Table 4).

Effect of Treatment Interruption With Clinical Efficacy

Using 6-week landmark analysis, the median OS among all patients requiring treatment interruption (either dose delay or cessation of PD-1 therapy) due to an irAE was 6.2 months (95% CI, 4.4-10.6) compared to 12.9 months (95% CI, 9.3-15.2) for those receiving PD-1 antibodies continuously ($P = .005$) (Figure 2A). A lower median OS for patients requiring treatment interruption was also obtained from 12-week landmark analysis (8.3 vs. 14.5 months, $P = .008$) (Figure 2B).

Analysis of treatment interruption due to pembrolizumab-associated irAE on clinical efficacy was limited by the small number of patients experiencing an irAE at the 6- and 12-week landmarks. Only 2 of 40 pembrolizumab-treated patients at the 6-week landmark and 3 of 39 patients alive at the 12-week landmark required treatment interruption due to irAE. No statistical association with treatment interruption and median OS in the pembrolizumab group was seen at the 6-week landmark ($P = .762$) or the 12-week landmark ($P = .264$)

Association of irAE With Clinical Outcomes

Using 6-week landmark analysis, nivolumab-treated patients who developed colitis had a lower median OS compared to those who did not (4.4 vs. 10.6 months, $P = .010$) (Figure 3A). In the nivolumab-treated group, no significant relationship with development of any irAE ($P = .785$), thyroid changes ($P = .397$), dermatitis ($P = .217$), pneumonitis ($P = .284$), hepatitis ($P = .138$), arthralgias ($P = .443$), or OS was observed (Supplemental Table 1). Twelve-week landmark analysis confirmed

Table 2 Cox Proportional Hazard Regression Analysis on Overall Survival of Whole Cohort at 6-Week Landmark Analysis

Characteristic	HR (95% CI)	*P*
Age (≥64 y vs. <64 y)	0.79 (0.55-1.13)	.196
Sex (male vs. female)	1.43 (1.00-2.04)	.051
Smoking Status		
Current vs. nonsmoker	1.25 (0.66-2.38)	.494
Former smoker vs. nonsmoker	1.05 (0.57-1.93)	.885
CCI score (≥3 vs. <3)	2.94 (1.89-4.58)	<.001
Histology (squamous vs. nonsquamous)	1.06 (0.66-1.69)	.817
ECOG PS (≥2 vs. 0/1)	2.82 (1.96-4.07)	<.001
Brain metastases	1.18 (0.69-2.00)	.549
Liver metastases	1.84 (1.12-3.03)	.017
***EGFR* Mutation**		
Negative vs. positive	0.60 (0.27-1.33)	.210
Unknown vs. positive	0.58 (0.23-1.49)	.261
irAE		
Grade 1/2 vs. no irAE	0.85 (0.50-1.42)	.526
Grade 3 or higher vs. no irAE	2.29 (1.05-4.98)	.036
Treatment (pembrolizumab vs. nivolumab)	0.68 (0.41-1.14)	.142

Abbreviations: CCI = Charlson comorbidity index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; HR = hazard ratio; irAE = immune-related adverse event.

Table 3 Distribution of irAEs

irAE	Nivolumab (N = 230)		Pembrolizumab (N = 41)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
Any	100 (43.5)	23 (10.0)	16 (39.0)	2 (4.9)
Hypothyroid	30 (13.0)	0	2 (4.9)	0
Dermatitis	31 (13.5)	5 (2.2)	4 (9.8)	1 (2.4)
Colitis	16 (7.0)	6 (2.6)	2 (4.9)	0
Hyperthyroid	8 (3.5)	0	2 (4.9)	0
Hepatitis	12 (5.2)	4 (1.7)	0	0
Arthralgias	8 (3.5)	0	5 (12.2)	0
Pneumonitis	11 (4.8)	4 (1.7)	6 (14.6)	0
Nephritis	7 (3.0)	1 (0.4)	1 (2.4)	0
Adrenal insufficiency	3 (1.3)	0	0	0
Diabetes	3 (1.3)	0	0	0
Hypophysitis	1 (0.4)	0	1 (2.4)	0
Pancreatitis	1 (0.4)	0	0	0
Neurologic	3 (1.3)	2 (0.9)	0	0
Cholangitis	1 (0.4)	1 (0.4)	1 (2.4)	0
Myopathy	2 (0.9)	0	0	0
Myositis	1 (0.4)	0	0	0
Mucositis	1 (0.4)	0	0	0
PPE	1 (0.4)	0	0	0
PMR	0	0	1 (2.4)	0
Vasculitis	1 (0.4)	1 (0.4)	0	0
ITP	0	0	1 (2.4)	1 (2.4)
Myocarditis	1 (0.4)	1 (0.4)	0	0

Data are presented as n (%).
Abbreviations: irAE = immune-related adverse event; ITP = idiopathic thrombocytopenic purpura; PMR = polymyalgia rheumatica; PPE = palmar plantar erythrodysesthesia.

that only colitis (compared to no colitis) correlated with a decreased median OS (6.2 months vs. 14.2 months, $P = .072$) (Figure 3B).

Multivariable analysis on OS at the 6-week landmark in the nivolumab group revealed CCI ≥ 3 ($P < .001$), ECOG PS ≥ 2 ($P < .001$), liver metastases ($P = .029$), and development of irAE greater than grade 2 versus no irAE were associated with decreased OS (Table 5).

In the pembrolizumab group, there was no statistical association between any irAE ($P = .869$), thyroid changes ($P = .362$), dermatitis ($P = .453$), colitis ($P = .394$), arthralgia ($P = .421$), and OS at the 6-week landmark (Supplemental Table 2). Similar results were obtained for the 12-week landmark analysis.

Six-week landmark multivariable analysis on OS in the pembrolizumab group, with *EGFR* mutation status removed as a result of collinearity with smoking status, was conducted on age, sex, smoking status, CCI score, ECOG PS, liver metastases, brain metastases, line of therapy for PD-1 antibody, and irAE grade 1/2 versus no irAE. No statistically significant associations with any of these variables and OS was found.

Discussion

In this multicenter retrospective chart review of 271 patients treated with nivolumab or pembrolizumab for advanced NSCLC, treatment interruption due to the development of irAE effected clinical efficacy. For the whole cohort and the nivolumab-treated group, individuals treated continuously had a higher median OS compared to those needing treatment interruption at the 6- and 12-week landmarks. While there was no difference in median OS in pembrolizumab recipients requiring treatment interruption, very few patients in this group needed treatment interruption at the 6- and 12-week landmarks.

Few data exist regarding the effect of treatment interruption due to irAE on efficacy outcomes in advanced NSCLC. A pooled analysis of randomized phase 2 and 3 trials for patients with advanced melanoma receiving induction nivolumab and ipilimumab followed by single-agent nivolumab found similar OS and PFS despite attenuation of the induction phase due to toxicity.[10] A retrospective review of patients with metastatic renal-cell carcinoma who discontinued PD-1 or PD-L1 antibodies after an initial response due to irAE revealed a prolonged time to progression.[22] Observations from these 2 studies support the hypothesis that immune-mediated adverse events signal activation of an immune reaction. In contrast, the present retrospective series identified a shorter median OS for patients with advanced NSCLC requiring drug interruption due to an irAE despite similar baseline characteristics and duration of PD-1 antibody therapy.

There are several potential reasons for discordant findings between our study and those involving patients with advanced melanoma and metastatic renal-cell carcinoma. First, it is possible that this association might differ depending on tumor type. Second, the exact treatment protocols varied; although our study involved PD-1 antibody monotherapy, all patients in the series of Schadendorf

Table 4 Baseline Demographic and Clinic Characteristics Stratified by Immune-Related Adverse Event–Related Treatment Interruption

Characteristic	No Treatment Interruption (N = 215)	Treatment Interruption (N = 56)	P[a]
Age (y)	63 (39-82)	66 (49-80)	.180
Sex			.134
Female	101 (47.0)	33 (58.9)	
Male	114 (53.0)	23 (41.1)	
ECOG PS at Initiation of PD-1 Ab			.628
0/1	150 (69.8)	37 (66.1)	
≥2	65 (30.2)	19 (33.9)	
Histologic Subtype			.488
Squamous	51 (23.7)	16 (28.6)	
Nonsquamous	164 (76.3)	40 (71.4)	
Smoking Status			.175
Nonsmoker	31 (14.4)	3 (5.4)	
Current smoker	73 (34.0)	20 (35.7)	
Former smoker	111 (51.6)	33 (58.9)	
Tumor Molecular Aberration			
EGFR mutation	14 (6.5)	2 (3.6)	.796
ALK rearrangement	2 (0.9)	1 (1.8)	.428
Brain metastases	31 (14.4)	5 (8.9)	.378
Liver metastases	29 (13.5)	4 (7.1)	.254
CCI score	6.0 (0.0-12.0)	6.0 (0.0-11.0)	.128
Treatment line			.863
First or second	163 (75.8)	42 (75.0)	
Third or higher	52 (24.2)	19 (25.0)	
No. of PD-1 treatments	8 (1-65)	8 (1-47)	.764

Data are presented as n (%) or median (range).
Abbreviations: ALK = anaplastic lymphoma kinase; CCI = Charlson comorbidity index; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; PD-1 Ab = programmed death 1 antibody; PD-L1 = programmed death ligand 1; RT = radiotherapy.
[a] *P* values reported for categorical variables are from Fisher exact test of independence, and those for continuous variables are from Mann-Whitney *U* test.

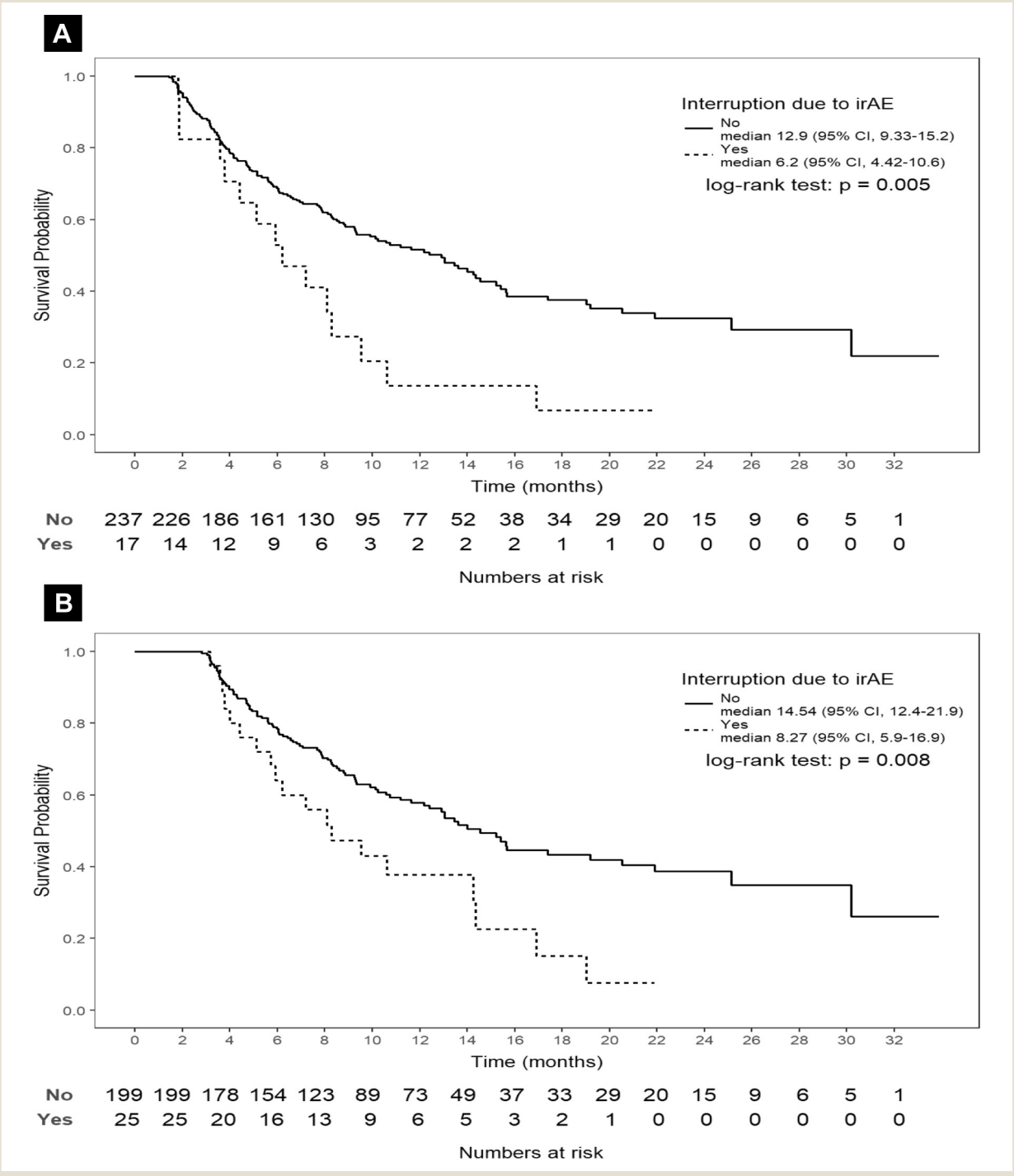
et al[10] received combination treatment with nivolumab and ipilimumab, and 36.8% of patients in the study by Martini et al[22] received combination therapy of PD-1 or PD-L1 antibody with another agent. Last, analysis assessing an association between physician reported irAE and efficacy end points depends on a clinician's practice of irAE reporting.[6]

In this retrospective series, the magnitude of benefit derived from PD-1 antibodies for those requiring treatment interruption was likely low and might be similar to chemotherapy. This underscores the need for a better biomarker to predict response to PD-1 antibodies for patients with incurable NSCLC. For example, in the CheckMate 057 study, nivolumab efficacy in advanced nonsquamous lung cancer was enhanced in patients with PD-L1 tumor expression > 1%, but responses were still observed in PD-L1–negative tumors.[4] In addition, intratumoral and intertumoral (primary vs. metastatic site) PD-L1 expression has been demonstrated.[23] As a result of limitations of PD-L1 immunohistochemical testing as a biomarker, tumor mutation burden, multiplex immunohistochemistry, and immune gene signatures are being investigated to better predict response to PD-1 inhibitors.[24]

Conflicting data exist with regard to an association of irAE with clinical efficacy of PD-1 antibodies in advanced NSCLC. Pneumonitis, dermatitis, and thyroid changes have been positively associated with survival outcomes.[11-13,15] In the present study, nivolumab-treated patients who developed colitis had worse median OS compared to patients who did not. We used landmark analysis to minimize the lead-time bias potentially associated with time-dependent factors. In a retrospective study using 6- and 8-week landmark analyses, Haratani et al[12] found that development of any irAE and dermatitis predicted longer median OS. Differences between studies might reflect different patient populations, misdiagnosis of irAE by the treating physician, or differences in irAE management (ie, suboptimal treatment of colitis would lead to more severe disease).

Pivotal nivolumab and pembrolizumab trials all excluded patients with ECOG PS > 1.[2-5] CheckMate 153 is an ongoing predominately community-based phase 3B/4 study of nivolumab monotherapy in advanced NSCLC; patients with a performance status of 2 had a lower 1-year OS than those with a performance status of 0 or 1.[25] The CCI score has also been identified as a poor prognostic factor in retrospective studies for patients with advanced NSCLC and *EGFR/ALK* wild-type disease.[26] In the present study, 31% of patients had ECOG PS > 2, and median CCI was 6. Importantly, on multivariate analysis of the whole cohort, poor ECOG PS and a high CCI score were the most powerful predictors of reduced OS. It is reassuring that the

Figure 2 Kaplan-Meier Curves for Patients Receiving PD-1 Ab Continuously and Those Requiring Treatment Interruption Due to irAE. (A) Six-week Landmark Analysis. (B) Twelve-week Landmark Analysis

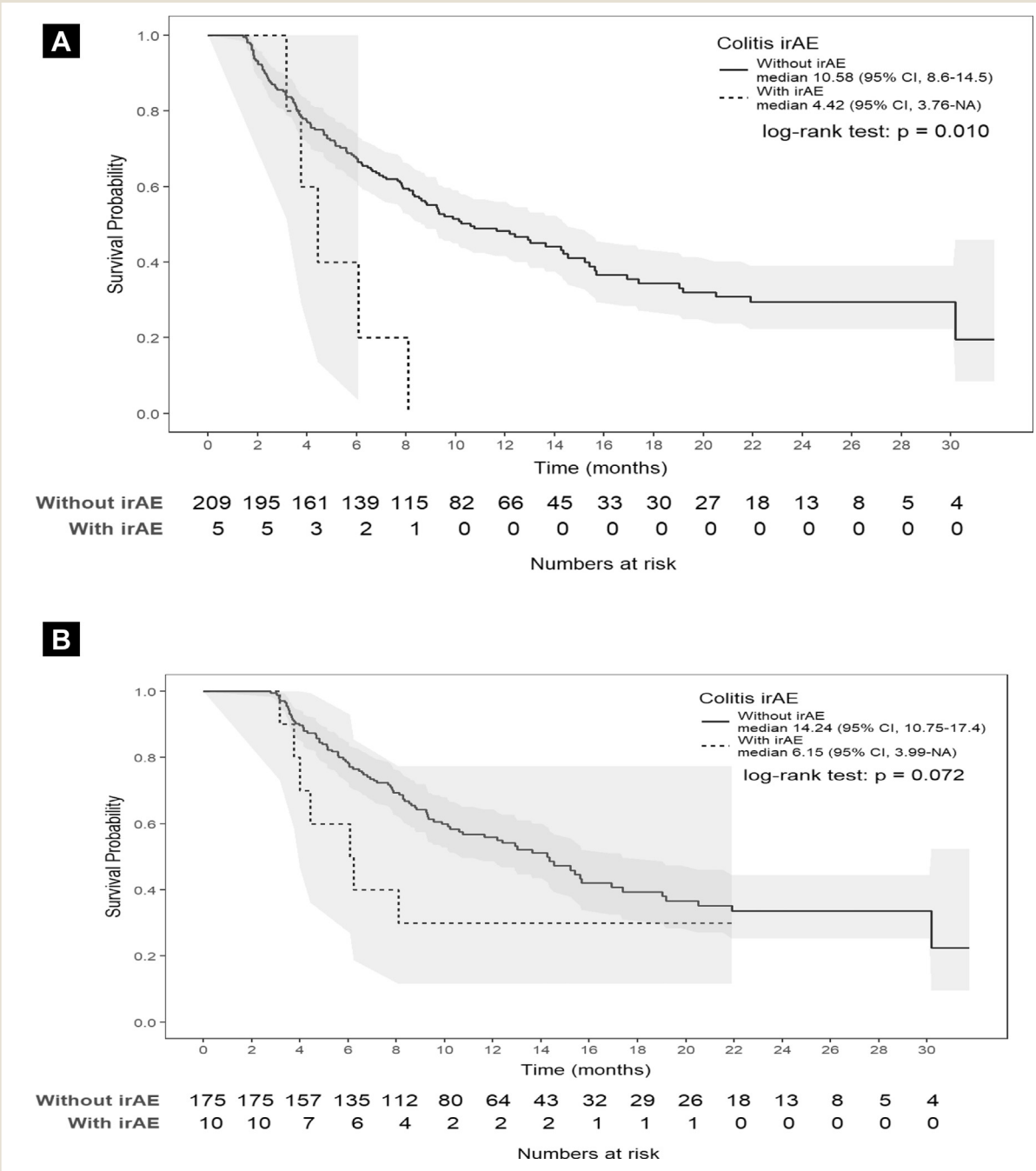


Abbreviations: Ab = antibody; irAE = immune-related adverse event; PD-1 = programmed cell death 1.

incidence of irAEs of grade 3 or higher was only 9.2%. It is also important to note that although the presence of brain metastases has traditionally been an adverse prognostic factor, this was not found in our multivariable analysis. However, all patients with brain metastases before initiation of PD-1 inhibitors underwent whole-brain radiotherapy or stereotactic radiotherapy, thereby increasing the likelihood of local control of the central nervous system.

Our study has some limitations. First, because all but one patient were treated outside of a clinical trial, the decision to delay or discontinue PD-1 inhibitors was dependent on a clinician's pattern of

Figure 3 Kaplan-Meier Survival Curves of Overall Survival for Nivolumab-Treated Patients Who Did and Did Not Develop Colitis. (A) Six-week Landmark Analysis. (B) Twelve-week Landmark Analysis. Shown Are 95% Confidence Intervals



practice; however, clinicians followed similar treatment algorithms, which advised when PD-1 antibodies should be held.[17,18] Second, because nivolumab-treated patients were seen in the clinic more frequently (every 2 weeks) than pembrolizumab-treated patients (every 3 weeks), there was an increased opportunity to diagnose irAE in the former group. Third, this study is retrospective in nature and thus subject to selection bias.

Conclusion

In the study cohort, patients who required treatment interruption due to irAE had a lower median OS compared to those treated continuously. Shorter OS seen with severe irAE might reflect the need for improved physician education in irAE treatment algorithms. Further study is required to identify clinical biomarkers that consistently predict early response to treatment.

Table 5 Cox Proportional Hazard Regression Analysis of Overall Survival of Nivolumab Group at 6 Week Landmark

Characteristic	HR (95% CI)	*P*
Age (≥64 y vs. <64 y)	0.83 (0.56-1.23)	.352
Sex (male vs. female)	1.27 (0.86-1.87)	.224
Smoking Status		
Current vs. nonsmoker	1.41 (0.73-2.75)	.307
Former vs. nonsmoker	1.10 (0.58-2.05)	.777
CCI score (≥3 vs. <3)	2.92 (1.82-4.70)	<.001
Histology (squamous vs. nonsquamous)	0.82 (0.48-1.39)	.459
ECOG PS (≥2 vs. 0/1)	2.76 (1.86-4.10)	<.001
Brain metastases	1.03 (0.58-1.82)	.921
Liver metastases	1.86 (1.07-3.24)	.029
Treatment line (≥third line vs. first/second line)	0.63 (0.40-0.98)	.040
***EGFR* Mutation**		
Negative vs. positive	0.44 (0.18-1.06)	.067
Unknown vs. positive	0.43 (0.15-1.25)	.120
irAE		
Grade3 1/2 vs. no irAE	0.74 (0.41-1.31)	.297
Grade 3 or higher vs. no irAE	2.53 (1.15-5.57)	.021

Abbreviations: CCI = Charlson comorbidity index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; HR = hazard ratio; irAE = immune-related adverse event.

Clinical Practice Points

- There is little published evidence on the effect of treatment interruption due to irAE on clinical efficacy of PD-1 receptors inhibitors in advanced NSCLC.
- Some studies have demonstrated that development of irAE can predict response in patients with advanced melanoma, metastatic renal-cell cancer, and NSCLC.
- In this retrospective chart review of patients with advanced NSCLC treated with pembrolizumab or nivolumab in British Columbia, the incidence of irAE was 42.8%. Pneumonitis and arthralgia were more common in pembrolizumab-treated patients.
- Patients needing treatment interruption because of an irAE had a lower median OS compared to those treated continuously in 6- and 12-week landmark analyses. In our series, patients requiring treatment interruption likely experienced only a small benefit from PD-1 inhibitors.
- Development of colitis in nivolumab recipients was associated with lower OS in 6- and 12-week landmark analyses.
- The association of severe irAE with decreased OS reflects a need for vigilance in early detection and aggressive management of irAE.

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Disclosure

The authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2018.09.005.

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Supplemental Table 1 Median OS for Nivolumab-Treated Patients With and Without irAE

Type of irAE	Median OS (mo) (95% CI)		*P*[a]
	With irAE	Without irAE	
Six-Week Landmark Analysis			
Any	8.3 (6.2-NR)	10.6 (8.6-14.5)	.78
Thyroid abnormality	15.2 (7.2-NR)	9.9 (8.3-14.2)	.39
Dermatitis	16.9 (8.27-NR)	9.9 (8.3-14.2)	.21
Pneumonitis	NR (NR-NR)	9.9 (8.3-14.2)	.28
Hepatitis	5.7 (1.9-NR)	10.2 (8.3-14.3)	.13
Colitis	4.4 (3.8-NR)	10.6 (8.6-14.5)	.01
Arthralgia	NR (8.27-NR)	10.1 (8.3-14.2)	.44
Twelve-Week Landmark Analysis			
Any	15.2 (13.6-NR)	12.4 (9.3-17.4)	.35
Thyroid abnormality	NR (15.2-NR)	12.9 (9.9-16.9)	.11
Dermatitis	19.0 (13.6-NR)	12.9 (9.5-15.7)	.12
Pneumonitis	19.0 (NR-NR)	13.6 (10.1-16.9)	.35
Hepatitis	9.5 (4.7-NR)	14.2 (10.6-17.4)	.42
Colitis	6.2 (4.0-NR)	14.2 (10.8-17.4)	.07
Arthralgia	NR (8.3-NR)	13.6 (10.2-16.9)	.43

Abbreviations: CI = confidence interval; irAE = immune-related adverse event; NR = not reached; OS = overall survival.
[a]Calculated by log-rank test.

Supplemental Table 2 Median OS for Pembrolizumab-Treated Patients With and Without irAE

Type of irAE	Median OS (mo) (95% CI)		*P*[a]
	With irAE	Without irAE	
Six-Week Landmark Analysis			
Any	13.5 (4.8-NR)	14.0 (10.6-NR)	.86
Thyroid abnormality	NR (NR-NR)	13.3 (10.6-NR)	.36
Dermatitis	13.5 (4.8-NR)	14.0 (10.6-NR)	.45
Colitis	3.2 (3.2-NR)	14.0 (11.2-NR)	.39
Arthralgia	NR (NR-NR)	13.5 (10.6-NR)	.41
Twelve-Week Landmark Analysis			
Any	13.5 (5.7-NR)	14.0 (11.2-NR)	.44
Thyroid abnormality	NR (NR-NR)	17.0 (13.5-11.2)	.36
Dermatitis	13.5 (4.8-NR)	14.0 (11.2-NR)	.39
Colitis	3.2 (3.2-NR)	14.0 (11.2-NR)	.32
Arthralgia	NR (NR-NR)	14.0 (11.2-NR)	NR

Abbreviations: CI = confidence interval; irAE = immune-related adverse event; NR = not reached; OS = overall survival.
[a]Calculated by log-rank test.