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Association of Extended Dosing Intervals or Delays in Pembrolizumab-based Regimens With Survival Outcomes in Advanced Non–small-cell Lung Cancer

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Abstract

The most cost-effective administration frequency of pembrolizumab in advanced non–small-cell lung cancer is unknown. We found that a significant proportion of these patients receive pembrolizumab-based regimens with extended intervals or delays in routine practice, with similar outcomes to those on label-specified 3-week interval treatments. Prospective evaluation of alternative dosing strategies is warranted to develop a more fiscally viable and patient-centered model.

Background: Besides modeling/simulation-based analysis, no post-approval studies have evaluated the optimal administration frequency of pembrolizumab in non–small-cell lung cancer (NSCLC). **Patients and Methods:** We performed a multicenter retrospective cohort study to evaluate the association between survival outcomes and treatment extensions/delays of pembrolizumab-based regimens in patients with advanced NSCLC. Those who had received at least 4 cycles in routine practice were divided into 2 groups: nonstandard (Non-Std, ≥ 2 cycles at intervals > 3 weeks + 3 days) and standard (Std, all cycles every 3 weeks or 1 cycle > 3 weeks + 3 days). **Results:** Among 150 patients, 92 (61%) were eligible for the study (Non-Std, 27; Std, 65). The reasons for patients with extensions/delays in the Non-Std group included: immune-related adverse events (irAEs) (33%), non–irAE-related medical issues (26%), and patient–physician preference (41%). The Non-Std group was more likely to have a higher programmed death-ligand 1 tumor proportion score, a higher number of treatment cycles, and pembrolizumab monotherapy. Univariate and 6-month landmark analyses showed longer median overall survival and progression-free survival in the Non-Std group compared with the Std group. After multivariable adjustment for confounding factors, there was no significant difference in overall survival (hazard ratio, 1.2; 95% confidence interval, 0.3–4.8; $P = .824$) or progression-free survival (hazard ratio, 2.6; 95% confidence interval, 0.7–9.6; $P = .157$) between the 2 groups. **Conclusion:** Our study shows that a significant proportion of patients with advanced NSCLC receive pembrolizumab-based regimens with extended intervals or delays in routine clinical practice and with similar outcomes to those receiving treatment at label-specified 3-week intervals. Given the durability of benefit seen and the potential for cost reduction and decreased infusion frequency in these patients, this requires validation in prospective trials.

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Introduction

The updated results of the KEYNOTE-001 study have confirmed the revolutionary impact of the anti-programmed death-1 agent pembrolizumab on outcomes of patients with advanced non-small-cell lung cancer (NSCLC) whose tumors lack actionable oncogenic drivers.¹⁻³ The widespread adoption of anti-programmed death-1 agents and durable responses seen in some patients have raised important questions regarding the optimal frequency of administration of these drugs, including the impact of treatment interruptions or discontinuations in routine clinical practice.⁴ Although immune-related adverse events (irAEs) have been associated with improved outcomes in NSCLC,^{5,6} a retrospective study in Canada suggested lower overall survival (OS) in patients receiving interrupted treatments owing to irAEs.⁷ Additionally, the lowest and least frequent dose of pembrolizumab that may permit maximal efficacy in advanced NSCLC is still unknown.^{4,8} Moreover, the financial and societal impacts of access to this durably efficacious therapy for this growing population necessitates thoughtful consideration of resource utilization and the patient care experience so as to afford an optimized and sustainable care paradigm for all those who may benefit.^{4,9,10}

Recent efforts to develop less frequent and more flexible dosing regimens have included the phase IIIb/IV CheckMate 384 study of nivolumab in advanced NSCLC, which confirmed similar efficacy and safety outcomes with 480 mg every 4 weeks compared with 240 mg every 2 weeks, as predicted by exposure-response evaluations.^{11,12} A modeling/simulation study, based on the established pharmacokinetic model of pembrolizumab from early developmental trials, predicted that a dose of 400 mg every 6 weeks would be equally as effective as the standard United States Food and Drug Administration (FDA)-approved dose of 200 mg every 3 weeks.¹³

However, clinical evaluations of these alternate dosing schemas have not yet been performed. We conducted a multicenter retrospective study to evaluate survival outcomes of patients with advanced NSCLC who were treated with pembrolizumab-based regimens at standard versus extended intervals in routine clinical practice.

Patients and Methods

In this retrospective cohort study, medical charts from 2 tertiary academic cancer centers, Beth Israel Deaconess Medical Center (BIDMC)/Harvard Medical School and Vidant Medical Center (VMC)/Brody School of Medicine at East Carolina University, were reviewed in accordance with research protocols approved by the respective institutional review boards. Patients with advanced NSCLC (defined as patients with stage IV or recurrent advanced disease, who were not candidates for curative intent treatment) who received pembrolizumab-based regimens (defined as first-time patients who were treated with pembrolizumab in the palliative care setting, either as monotherapy or along with chemotherapy) for at least 4 cycles in routine practice outside clinical trials at either BIDMC or VMC between February 1, 2016 and April 5, 2019 were eligible. Those who started their first pembrolizumab-based regimen outside these 2 centers were excluded from the study. Patients eligible for the study were divided into 2 groups: (1) the nonstandard group (Non-Std: those receiving pembrolizumab 200

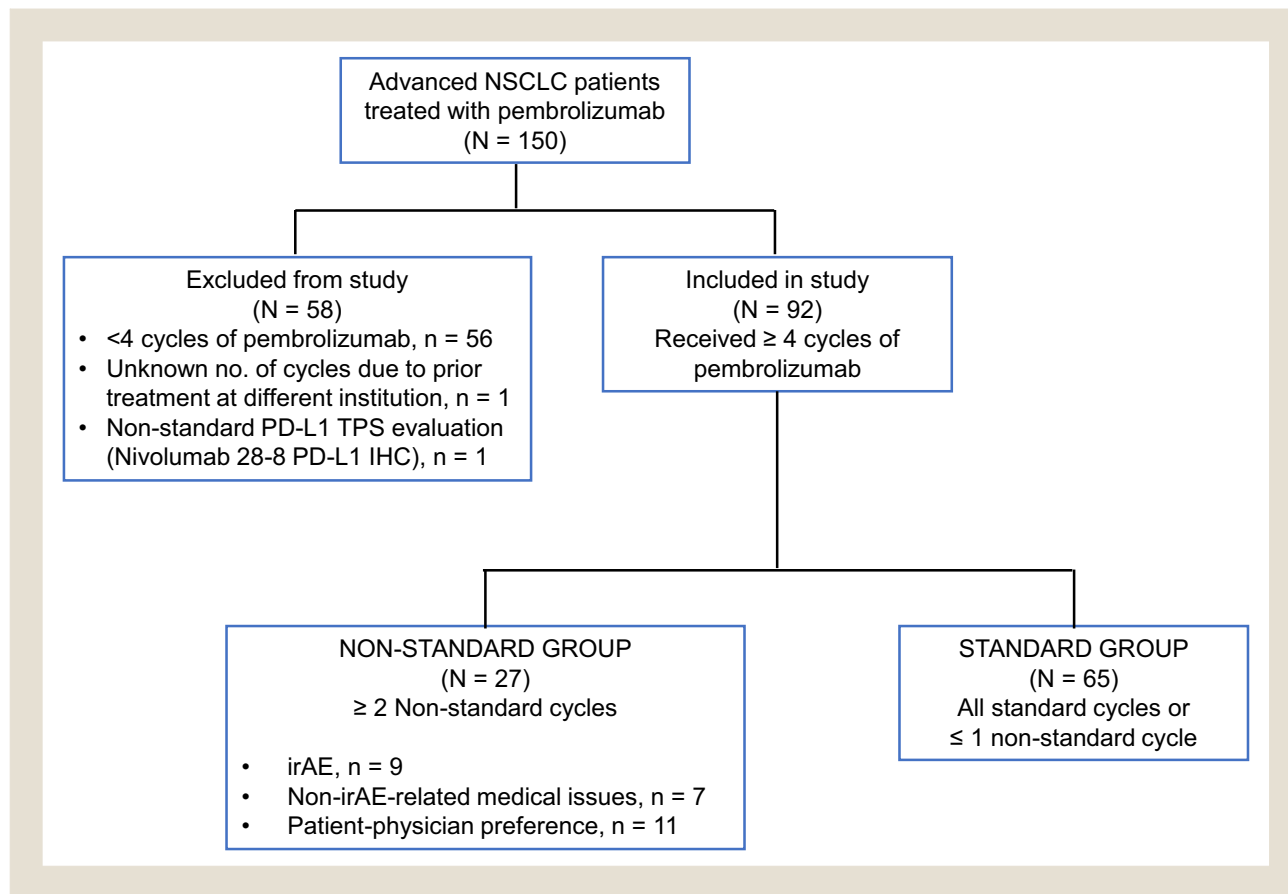
mg for ≥ 2 cycles at intervals > 3 weeks + 3 days for any reason), and (2) the standard group (Std: either all treatment cycles at FDA-approved dose interval or up to 1 cycle at interval > 3 weeks + 3 days for any reason). The objective of this study was to evaluate if patients with advanced NSCLC belonging to the Non-Std group had worse OS or progression-free survival (PFS) compared with the Std group.

Patient data was collected on demographics, clinicopathologic characteristics, treatment regimen details, and irAEs. Patient characteristics such as age and Eastern Cooperative Oncology Group performance status, survival time, and duration of response were calculated from the start of first pembrolizumab-based treatment, until progression or switch to alternative/additional therapy. Tumor molecular profile and mutational burden were evaluated in these patients by different multiplex next-generation sequencing platforms as well as polymerase chain reaction and fluorescence in-situ hybridization for individual mutations/rearrangements. Disease response was evaluated by thoracic radiologists using the immune Response Evaluation Criteria in Solid Tumors (iRECIST).¹⁴ Descriptive tables were generated, depicting proportions for categorical variables and median (with range) for noncategorical variables. The Fisher exact and Wilcoxon rank sum tests were used to calculate 2-sided *P* values for categorical and continuous outcomes, respectively. Kaplan-Meier survival curves and the log-rank test were employed for analysis of censored survival outcomes. Six-month landmark analysis was performed to account for immortal time bias. Univariate and multivariable regression to adjust for confounding variables were performed using Cox proportional hazards model. A Swimmer plot was generated to depict the duration of response from the first nonstandard cycle in the Non-Std group. A 2-sided *P* value $< .05$ was considered significant. Adjustments for multiple comparisons were not made owing to the exploratory nature of this analysis. Graph creation and statistical analysis were performed using Microsoft Excel and Stata/IC v15.1 software.

Results

Of 150 patient charts reviewed from both centers, 92 (61%) patients had received at least 4 cycles of pembrolizumab-based regimens and were eligible for the study (Figure 1, which demonstrates distribution of screened patients, and Supplemental Table 1 [in the online version], which demonstrates characteristics of included and excluded patients). Twenty-seven (29%) patients were classified in the Non-Std group, whereas 65 (71%) belonged to the Std group. Among the Non-Std group patients, 16 had treatment delays owing to irAEs (9; 33%) or non-irAE-related medical issues (7; 26%) (see Supplemental Table 2 in the online version). Eleven (41%) patients opted to receive treatments at extended dosing intervals after a detailed discussion with their physicians. Table 1 summarizes the patient characteristics of the Non-Std and Std groups. Patients in the Std group were more likely to receive pembrolizumab along with chemotherapy (Non-Std: 29% vs. Std: 66%; *P* = .002) and have tumors with lower programmed death-ligand 1 tumor proportion score (*P* = .01). Patients in the Non-Std group were more likely to have a higher number of treatment cycles (Non-Std: 14 vs. Std: 6; *P* $< .0001$).

Figure 1 Distribution of Patients With Advanced NSCLC Screened in the Study



Abbreviations: IHC = Immunohistochemistry; irAE = immune-related adverse event; NSCLC = non-small-cell lung cancer; PD-L1 = programmed death-ligand 1; TPS = tumor proportion score.

The median OS was not reached (NR) in the Non-Std group and was significantly longer compared with the Std group by univariate analysis (Std: 15.4 months; 95% confidence interval [CI], 9.0 months to NR vs. Non-Std: NR; 95% CI, NR) (Figure 2A, Supplemental Table 3 [in the online version]). The median PFS was also significantly longer in the Non-Std group compared with the Std group by univariate analysis (Std: 7.0 months; 95% CI, 5.1-8.8 months vs. Non-Std: 23.3 months; 95% CI, 14.6 months to NR) (Figure 2B, Supplementa Table 4 [in the online version]). Six-month landmark analyses continued to show significant differences in both OS (Std: 34.9 months; 95% CI, 15.4 months to NR vs. Non-Std: NR; 95% CI, NR) and PFS (Std: 11.8 months; 95% CI, 8.8 months to NR vs. Non-Std: NR; 95% CI, 14.6 months to NR) between the 2 groups (Figure 2C-D). However, after adjustment with multivariable regression (stratified by immune-related adverse events owing to its time-variant nature), no significant differences were seen in OS (hazard ratio [HR] for death, 1.2; 95% CI, 0.3-4.8) or PFS (HR for disease progression or death, 2.6; 95% CI, 0.7-9.6) between the Non-Std and Std groups (Tables 2 and 3). Swimmers' plots for patients belonging to the Non-Std group showed that most patients received their first nonstandard cycle within 6 months of start of therapy, with most having sustained responses (Figure 3). Univariate analyses of OS and PFS by the 3 predominant indications for nonstandard dosing in the Non-Std

group compared with the Std group showed statistically significant differences favoring the Non-Std subgroups — except for OS relating to the patient-physician preference (see Supplemental Figure 1 in the online version).

Discussion

We report here the real-world outcomes of patients with advanced NSCLC receiving pembrolizumab-based regimens with extended intervals or treatment delays owing to indications commonly encountered in routine clinical practice: irAEs, treatment-unrelated medical issues, and/or individual care preferences. Within the limitations discussed below, these patients had comparable outcomes with those who either received all (or up to 1 delayed cycle of) pembrolizumab at the FDA-approved label dosage of 200 mg every 3 weeks. We acknowledge that our results are hypothesis-generating only, but relevant in an arena where no other well-vetted data exists.

Most early pharmacokinetic and pharmacodynamic studies from phase I clinical trials of pembrolizumab evaluated doses between 2 and 10 mg/kg every 2 to 3 weeks.^{2,15-17} These were the basis of a modeling/simulation study that evaluated the exposure-response relationship with extended pembrolizumab dosing interval of 6 weeks, albeit with a higher dose of 400 mg¹³; this dosing schema was approved by the European Commission and recently by the

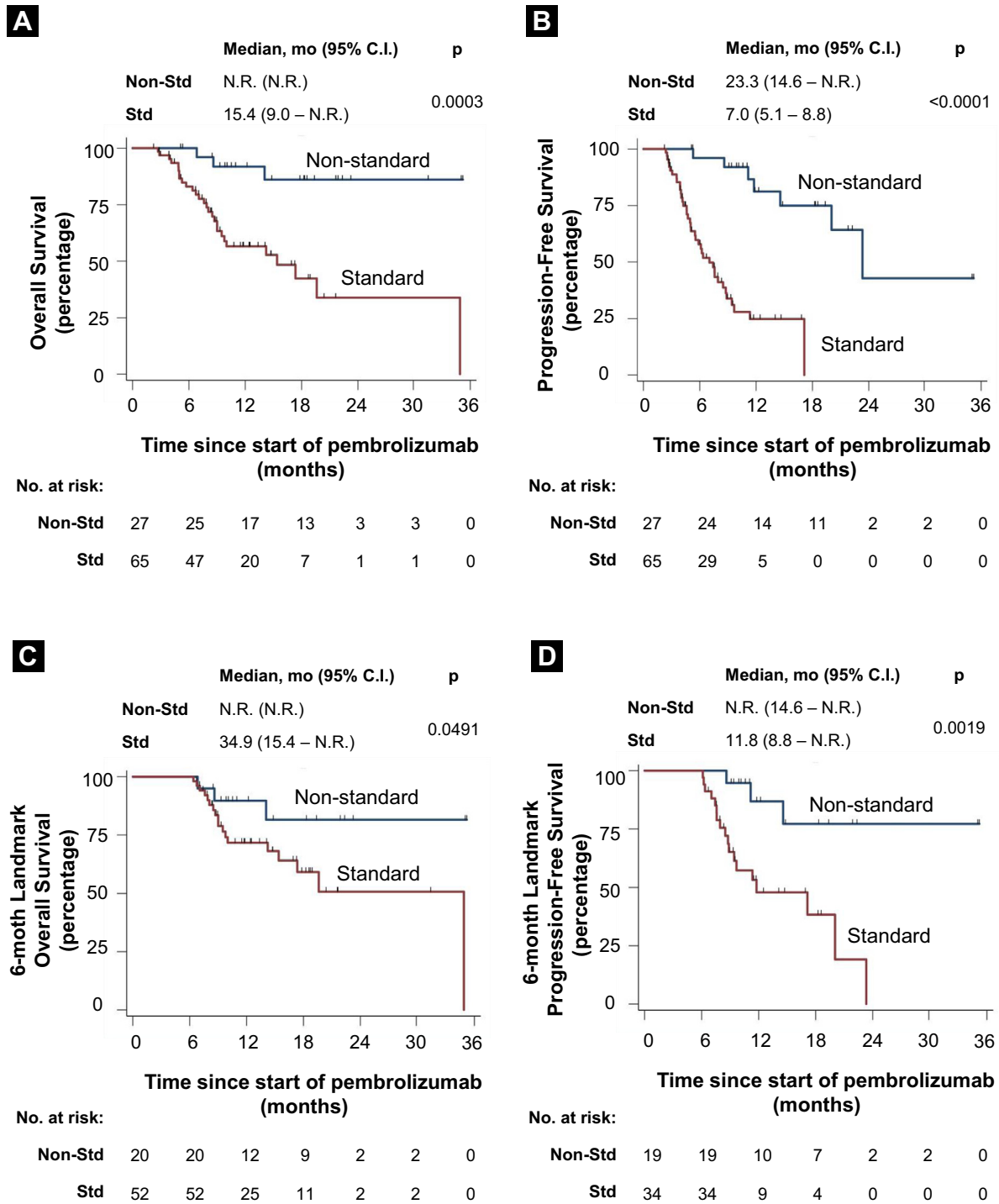
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Table 1 Patient Characteristics in the Nonstandard Versus Standard Groups

	All Patients (N = 92)	Standard Group (N = 65)	Nonstandard Group (N = 27)
Clinico-pathologic characteristics			
Median age, y (range)	64.5 (37-87)	64 (49-87)	66 (37-87)
Female gender	44 (48)	31 (48)	13 (48)
Smoking status, ever	84 (91)	58 (89)	26 (96)
ECOG PS			
0-1	75 (82)	54 (83)	21 (78)
≥ 2	17 (18)	11 (17)	6 (22)
Histology			
Non-squamous	70 (76)	49 (75)	21 (78)
Squamous	15 (16)	11 (17)	4 (15)
Poorly differentiated	7 (8)	5 (8)	2 (7)
Driver mutation			
<i>KRAS</i>	33 (36)	26 (40)	7 (26)
<i>EGFR</i>	6 (7)	3 (5)	3 (11)
Others	3 (3)	2 (3)	1 (4)
None identified	40 (43)	27 (41)	13 (48)
Not assessed	10 (11)	7 (11)	3 (11)
PD-L1 TPS, %			
<1	24 (26)	22 (34)	2 (7)
1-49	17 (18)	9 (14)	8 (30)
≥50	42 (46)	28 (43)	14 (52)
Not assessed	9 (10)	6 (9)	3 (11)
TMB, mut/mB			
<10	20 (22)	16 (25)	4 (15)
≥10	30 (32)	19 (29)	11 (41)
Not assessed	42 (46)	30 (46)	12 (44)
Treatment characteristics			
Line of pembrolizumab			
First line	65 (71)	50 (77)	15 (56)
≥Second line	27 (29)	15 (23)	12 (44)
Treatment			
Monotherapy	41 (45)	22 (34)	19 (71)
With chemotherapy	51 (55)	43 (66)	8 (29)
Treatment center			
BIDMC	47 (51)	29 (45)	18 (67)
VMC	45 (49)	36 (55)	9 (33)
Median no. of treatment cycles (range)	8 (4-41)	6 (4-20)	14 (6-41)
Best response			
Progression	7 (8)	6 (9)	1 (4)
Clinical benefit	83 (90)	57 (88)	26 (96)
CR	15 (16)	12 (19)	3 (11)
PR	40 (44)	25 (38)	15 (56)
SD	28 (30)	20 (31)	8 (30)
Not available	2 (2)	2 (3)	-
Any grade irAE, yes	54 (59)	35 (54)	19 (70)
≥Grade 3 irAE, yes	28 (30)	21 (32)	7 (26)
Systemic immunosuppression, yes	41 (45)	29 (45)	12 (44)

Abbreviations: BIDMC = Beth Israel Deaconess Medical Center; CR = complete response; ECOG = Eastern Cooperative Oncology Group; irAE = immune-related adverse events; PR = partial response; PS = performance status; SD = stable disease; TMB = tumor mutational burden; TPS = tumor proportion score; VMC = Vidant Medical Center. Data are shown as n (%), unless specified.

Figure 2 Univariate Kaplan-Meier Survival Curves in Patients With Advanced NSCLC Belonging to Nonstandard Versus Standard Groups for Overall Survival (A), Progression-free Survival (B), 6-month Landmark Overall Survival (C), and 6-month Landmark Progression-free Survival (D)



Abbreviations: CI = Confidence interval; mo = months; Non-Std = nonstandard; NR = not reached; NSCLC = non-small-cell lung cancer; Std = standard.

FDA.^{18,19} Whether extending pembrolizumab dosing intervals while keeping the dose at 200 mg will lead to the same predicted efficacy and safety has not been studied yet. Our data provides

rationale for further evaluation of extended dosing intervals of pembrolizumab, particularly in patients with disease response or stabilization after the first 4 treatment cycles. This may be a more

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Table 2 Multivariable Adjustment for Confounding Factors for Overall Survival by Cox Proportional Hazards Regression Model Stratified by Immune-related Adverse Events

	HR for Death (95% CI)	P
Standard vs. nonstandard group	1.2 (0.3-4.8)	.824
ECOG PS \geq 2 vs. 0-1	2.4 (0.9-5.9)	.066
Pembrolizumab alone vs. along with chemotherapy	1.4 (0.6-3.3)	.446
< 50% vs. \geq 50% PD-L1 TPS	0.8 (0.3-1.9)	.591
No. treatment cycles	0.8 (0.6-0.9)	.001

Abbreviations: CI = Confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PD-L1 = programmed death-ligand 1; PS = performance status; TPS = tumor proportion score.

Bold value is significant.

fiscally and logistically viable model, while improving flexibility and patient experience.

Recent pharmacoeconomic analyses comparing alternative dosing strategies of pembrolizumab (including weight-based dosing) to FDA-approved labels have estimated major cost savings for the health system with a personalized approach.^{20,21} Randomized non-inferiority clinical trials designed with Bayesian methods would be the gold-standard for evaluating these extended dosing regimens in an effective and cost-efficient manner.^{9,22-24} Alternatively, therapeutic drug monitoring for personalized dosing — as commonly used for antibiotics and immunosuppressive agents — to achieve plasma or serum drug concentrations within a known therapeutic range is another potential strategy that can be employed in prospective studies to minimize financial toxicity from drug and pharmacy costs in this growing population.^{9,25} It would also be prudent to take into account the time-dependent reduction in clearance of immune checkpoint inhibitors in these studies.^{26,27}

Limitations of this study include retrospective analysis, small sample size, confounding by indication, exclusion of patients who did not receive at least 4 pembrolizumab-based treatment cycles, and inclusion of patients treated only at tertiary academic cancer centers. These results are not applicable to patients whose disease progresses earlier in the treatment course and those being treated in other practice settings. Even though we employed a 6-month landmark survival analysis and multivariable regression to account for the guaranteed time bias and confounding variables, respectively, these biases persist. These findings require vetting in a large prospective manner. Moreover, it is not possible to draw any definitive conclusions when comparing the 3 predominant subgroups of the Non-Std group to the Std group owing to the small sample sizes. Tumor mutation burden was not included in the final adjusted model, as it was available for only approximately 50% of the patients and was not measured with a uniform assay.

Conclusions

To the best of our knowledge, this is the first study to describe outcomes of patients with advanced NSCLC receiving pembrolizumab-based regimens at extended intervals owing to real-world situations commonly faced in routine clinical practice and unprecedented circumstances such as the COVID-19 pandemic. Within the limitations described above, our study provides rationale

Table 3 Multivariable Adjustment for Confounding Factors for Progression-free Survival by Cox Proportional Hazards Regression Model Stratified by Immune-related Adverse Events

	HR for Disease Progression or Death (95% CI)	P
Standard vs. nonstandard group	2.6 (0.7-9.6)	.157
Never vs. current/former smoker	4.2 (1.6-11.3)	.004
Pembrolizumab alone vs. along with chemotherapy	2.7 (1.2-6.2)	.016
< 50% vs. \geq 50% PD-L1 TPS	0.9 (0.4-2.1)	.873
ECOG PS \geq 2 vs. 0-1	0.8 (0.4-1.9)	.700
No. of treatment cycles	0.7 (0.6-0.8)	<.001

Abbreviations: CI = Confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PD-L1 = programmed death-ligand 1; PS = performance status; TPS = tumor proportion score.

Bold values are significant.

for prospectively evaluating the administration of the lowest and least frequent efficacious dose of pembrolizumab, particularly for patients with demonstrated disease stability or response for the first 3 to 6 months.

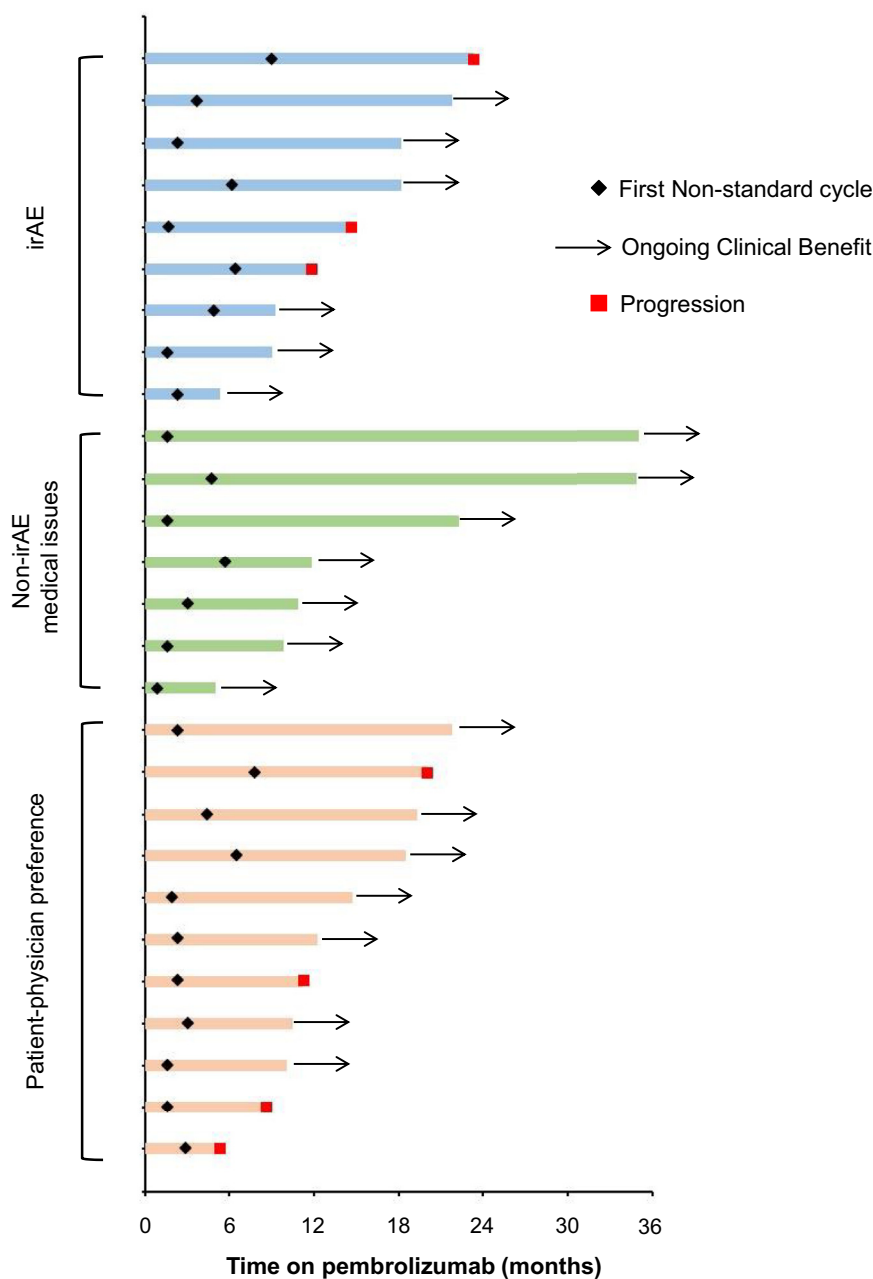
Clinical Practice Points

- The most cost-effective administration frequency of pembrolizumab in advanced NSCLC has not been evaluated in clinical trials. Based on a modeling/simulation study, the dosing schedule of pembrolizumab at 400 mg every 6 weeks has been approved by the European Commission and the FDA.
- In this multicenter retrospective cohort study, we found that a significant proportion of patients with advanced NSCLC receive pembrolizumab-based regimens with extended intervals or delays in routine clinical practice owing to irAEs, medical issues, and patient-physician preferences.
- We found that these treatment delays or extended dosing intervals were not associated with worse outcomes after multivariable adjustment for confounding factors in the patients with advanced NSCLC who had received at least 4 cycles of pembrolizumab-based regimens.
- To the best of our knowledge, this is the first study to describe outcomes of patients with advanced NSCLC receiving pembrolizumab-based regimens at extended intervals owing to real-world situations commonly faced in routine clinical practice.
- Prospective evaluation of alternative dosing strategies in randomized non-inferiority clinical trials, with attention to time-dependent reduction in clearance of pembrolizumab and potential incorporation of personalized dosing with therapeutic drug monitoring is warranted.
- Alternative dosing strategies may provide a more fiscally and logistically viable model, while improving flexibility and patient experience.

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Figure 3 Swimmer's Plot Showing Time on Pembrolizumab Treatment After First Nonstandard (Extended or Delayed) Pembrolizumab Cycle in the Nonstandard Group With Patients Distributed by the Indication Subgroups



Abbreviation: irAE = Immune-related adverse event.

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Disclosure

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Supplemental Data

Supplemental tables and figure accompanying this article can be found in the online version at <https://doi.org/10.1016/j.clc.2020.05.028>

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Supplemental Data

Supplemental Table 1 Patient Characteristics of the Screened Population		
	Included Patients (N = 92)	Excluded Patients (N = 58)
Clinico-pathologic characteristics		
Median age, y (range)	64.5 (37-87)	69 (33-87)
Female gender	44 (48)	31 (53)
Smoking status, ever	84 (91)	52 (90)
ECOG PS		
0-1	75 (82)	27 (47)
≥2	17 (18)	28 (48)
Not reported	0 (0)	3 (5)
Histology		
Non-squamous	70 (76)	45 (78)
Squamous	15 (16)	9 (15)
Poorly differentiated	7 (8)	4 (7)
Driver mutation		
<i>KRAS</i>	33 (36)	19 (33)
<i>EGFR</i>	6 (7)	3 (5)
Others	3 (3)	3 (5)
None identified	40 (43)	25 (43)
Not assessed	10 (11)	8 (14)
PD-L1 TPS, %		
<1	24 (26)	8 (14)
1-49	17 (18)	15 (26)
≥50	42 (46)	31 (53)
Not assessed	9 (10)	4 (7)
TMB, mut/mB		
<10	20 (22)	14 (24)
≥10	30 (32)	11 (19)
Not assessed	42 (46)	33 (57)
Treatment characteristics		
Line of pembrolizumab		
First line	65 (71)	39 (67)
≥Second line	27 (29)	19 (33)
Treatment		
Monotherapy	41 (45)	35 (60)
With chemotherapy	51 (55)	22 (38)
Not known	0 (0)	1 (2)
Treatment center		
BIDMC	47 (51)	34 (59)
VMC	45 (49)	24 (41)
Median no. treatment cycles (range)	8 (4-41)	2 (1-3)
Any grade irAE, yes	54 (59)	16 (28)
≥Grade 3 irAE, yes	28 (30)	12 (21)
Systemic immunosuppression for irAE, yes	41 (45)	16 (28)

Abbreviations: BIDMC = Beth Israel Deaconess Medical Center; CR = complete response; ECOG = Eastern Cooperative Oncology Group; irAE = immune-related adverse events; PD-L1 = programmed death-ligand 1; PS = performance status; TMB = tumor mutational burden; TPS = tumor proportion score; VMC = Vidant Medical Center.
Data shown as n (%), unless specified.

Extended-Interval Dosing of Pembrolizumab in Lung Cancer

Supplemental Table 2 Reasons for Delays or Extensions in the Nonstandard Group

Serial No.	Subgroup	Reason(s)
1	irAE	Arthritis, holidays
2	irAE	Synovitis, patient-physician preference
3	irAE	Hospitalization for adrenal insufficiency
4	irAE	Fatigue
5	irAE	Pneumonitis
6	irAE	Pneumonitis, adrenal insufficiency, fatigue
7	irAE	Toxic epidermal necrolysis
8	irAE	Thyroiditis
9	irAE	Pneumonitis, patient requested treatment break
10	Non-irAE medical issues	Hospitalization for pneumonia, missed restaging scans, insurance issues, family issues
11	Non-irAE medical issues	Missed visits owing to depression, transportation issues
12	Non-irAE medical issues	Hospitalization for postoperative wound infection
13	Non-irAE medical issues	Pneumonia, travel plans, holidays, switched treatment to every 6 weeks after completing 2 years
14	Non-irAE medical issues	Pneumonia, Gastrointestinal issues, travel plans
15	Non-irAE medical issues	Open draining chest wall wound, holidays
16	Non-irAE medical issues	Respiratory symptoms (not pneumonitis), hospitalization for atrial fibrillation with rapid ventricular rhythm
17	Preference	Patient-physician preference
18	Preference	Patient-physician preference
19	Preference	Patient-physician preference
20	Preference	Patient-physician preference, insurance issues
21	Preference	Patient-physician preference, travel plans
22	Preference	Patient-physician preference, death in family, travel plans
23	Preference	Patient-physician preference, travel plans
24	Preference	Patient-physician preference, travel plans, scheduling issues owing to preference to see primary oncologist only
25	Preference	Patient-physician preference, holidays
26	Preference	Patient-physician preference, patient cancelled multiple appointments
27	Preference	Patient-physician preference

Abbreviation: irAE = Immune-related adverse events.

Supplemental Table 3 Univariate Analysis of Overall Survival by Cox Proportional Hazards Regression Model

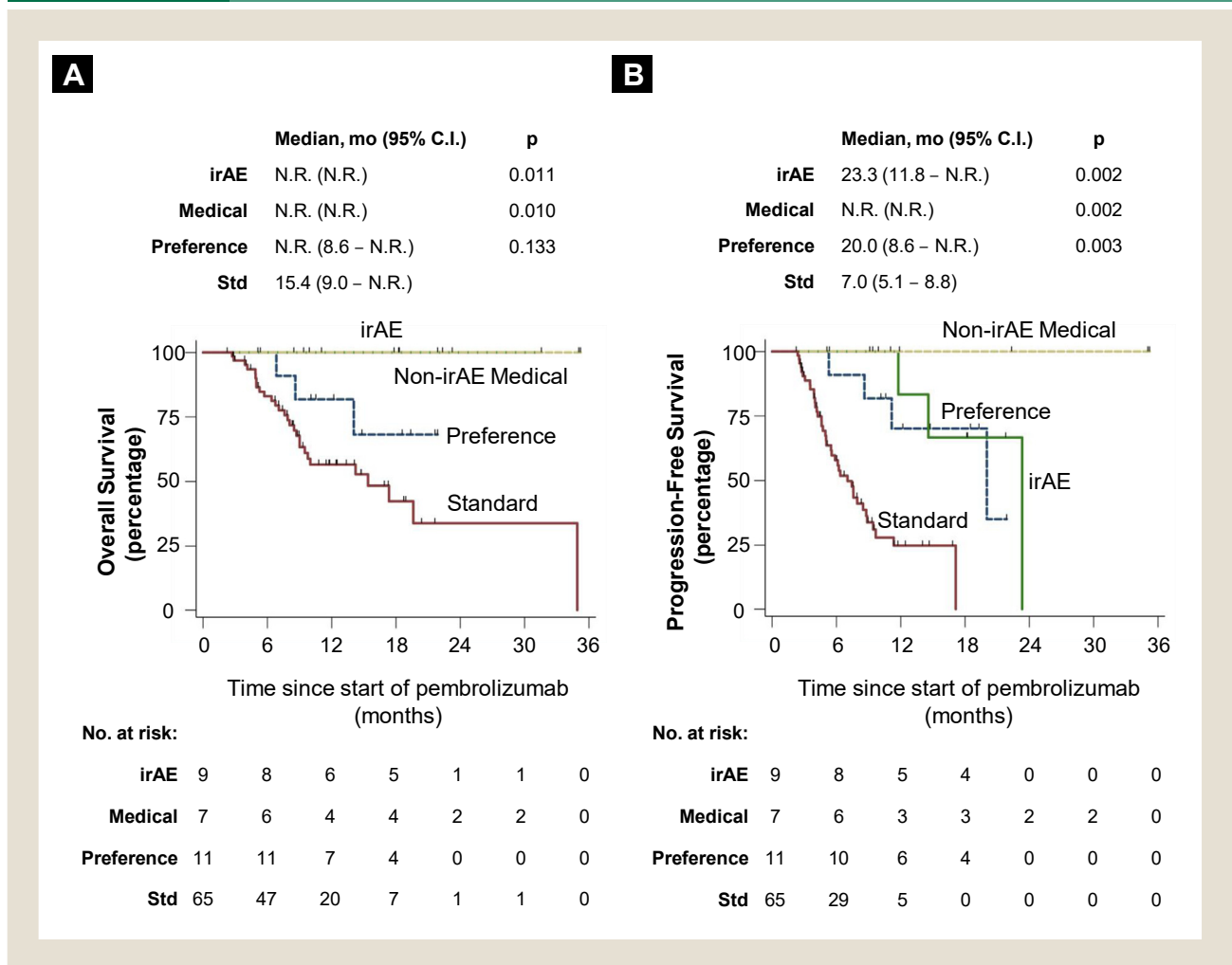
	HR for Death (95% CI)	P
Standard vs. nonstandard group	6.9 (2.1-22.9)	.002
Age (years)	1.0 (0.9-1.1)	.060
Never vs. current/former smoker	1.5 (0.6-4.0)	.85
ECOG PS \geq 2 vs. 0-1	1.8 (0.8-3.9)	.175
<50% vs. \geq 50% PD-L1 TPS	1.4 (0.7-2.9)	.90
Later vs. first line of therapy	0.5 (0.2-1.3)	.167
Pembrolizumab alone vs. along with chemotherapy	1.0 (0.5-2.1)	.944
No. of treatment cycles	0.8 (0.7-0.9)	<.001
Absence vs. presence of any grade irAE	2.2 (1.1-4.5)	.030
VMC vs. BIDMC	0.8 (0.4-1.7)	.615

Abbreviations: BIDMC = Beth Israel Deaconess Medical Center; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; irAE = immune-related adverse events; PD-L1 = programmed death-ligand 1; PS = performance status; TPS = tumor proportion score; VMC = Vidant Medical Center. Bold values are significant.

Supplemental Table 4 Univariate Analysis of Progression-free Survival by Cox Proportional Hazards Regression Model

	HR for Disease Progression or Death (95% CI)	P
Standard vs. nonstandard group	8.5 (3.2-22.4)	<.001
Age, y	1.0 (0.9-1.0)	.411
Never vs. current/former smoker	1.9 (0.8-4.7)	.131
ECOG PS ≥ 2 vs. 0-1	0.9 (0.6-1.6)	.964
<50% vs. $\geq 50\%$ PD-L1 TPS	1.2 (0.7-2.3)	.494
Later vs. first line of therapy	0.6 (0.3-1.3)	.190
Pembrolizumab alone vs. along with chemotherapy	0.8 (0.4-1.5)	.490
No. treatment cycles	0.7 (0.7-0.8)	<.001
Absence vs. presence of any grade irAE	1.5 (0.8-2.8)	.150
VMC vs. BIDMC	0.7 (0.4-1.3)	.242

Abbreviations: BIDMC = Beth Israel Deaconess Medical Center; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; irAE = immune-related adverse events; PD-L1 = programmed death-ligand 1; PS = performance status; TPS = tumor proportion score; VMC = Vidant Medical Center. Bold values are significant.

Supplemental Figure 1 Univariate Survival Curves in Patients With Advanced NSCLC Belonging to the Standard Group Versus Subgroups of the Nonstandard Group for Overall Survival (A) and Progression-free Survival (B)

Abbreviations: CI = Confidence interval; irAE = immune-related adverse event; NR = not reached; NSCLC = non-small-cell lung cancer; Std = standard.