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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 development 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).
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, Supplemental 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. 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 mg; this dosing schema was approved by the European Commission and recently by the
### Table 1 Patient Characteristics in the Nonstandard Versus Standard Groups

| Clinico-pathologic characteristics | All Patients (N = 92) | Standard Group (N = 65) | Nonstandard Group (N = 27) |
|------------------------------------|----------------------|-------------------------|---------------------------|
| 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                    |                      |                         |                           |
| KRAS                               | 33 (36)              | 26 (40)                 | 7 (26)                    |
| EGFR                               | 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.
FDA.\textsuperscript{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

| Comparison                          | HR for Death (95% CI) | P   |
|-------------------------------------|-----------------------|-----|
| Standard vs. nonstandard group       | 1.2 (0.3-4.8)         | .824|
| ECOG PS ≥ 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. ≥ 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.

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

| Comparison                          | 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. ≥ 50% PD-L1 TPS           | 0.9 (0.4-2.1)                              | .873|
| ECOG PS ≥ 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.

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. 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. Moreover, 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. It would also be prudent to take into account the time-dependent reduction in clearance of immune checkpoint inhibitors in these studies.

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-Standard group to the Standard 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 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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Supplemental Data

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

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### Supplemental Table 1  Patient Characteristics of the Screened Population

| Clinico-pathologic characteristics | Included Patients (N = 92) | Excluded Patients (N = 58) |
|------------------------------------|---------------------------|---------------------------|
| 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                    |                           |                           |
| KRAS                               | 33 (36)                   | 19 (33)                   |
| EGFR                               | 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.
## 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 ≥ 2 vs. 0-1                  | 1.8 (0.8-3.9)         | .175 |
| <50% vs. ≥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. ≥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.

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**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)

**A**

|                              | Median, mo (95% C.I.) | p      |
|------------------------------|----------------------|--------|
| irAE                         | N.R. (N.R.)          | 0.011  |
| Medical Preference           | N.R. (8.6 – N.R.)    | 0.133  |
| Std                          | 15.4 (9.0 – N.R.)    |        |

**B**

|                              | Median, mo (95% C.I.) | p      |
|------------------------------|----------------------|--------|
| irAE                         | 23.3 (11.8 – N.R.)   | 0.002  |
| Medical Preference           | 20.0 (8.6 – N.R.)    | 0.003  |
| Std                          | 7.0 (5.1 – 8.8)      |        |

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