ORIGINAL ARTICLE

First-Line Pembrolizumab Plus Chemotherapy for Advanced Squamous NSCLC: Real-World Outcomes at U.S. Oncology Practices

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ABSTRACT

Introduction: Pembrolizumab plus carboplatin and (nab-) paclitaxel (pembrolizumab-chemotherapy) is currently an approved and recommended systemic therapy for patients with previously untreated advanced squamous NSCLC. This retrospective study evaluated real-world time on treatment (rwToT) and overall survival (OS) among patients with advanced squamous NSCLC treated with first-line pembrolizumab-chemotherapy at oncology practices in the United States.

Methods: Using a real-world database, we selected adult patients with newly diagnosed or recurrent advanced squamous NSCLC (unresectable stages IIIB, IIIC, or IV) and good performance status (Eastern Cooperative Oncology Group 0–1) who initiated first-line pembrolizumab-chemotherapy from November 1, 2018, to May 31, 2020. The Kaplan-Meier method was used to determine rwToT and OS overall and by programmed death-ligand 1 (PD-L1) expression. Data cutoff was October 31, 2021.

Results: Of 364 eligible patients, 243 (67%) were men; median age was 70 (range: 43–84) years; and PD-L1 expression was greater than or equal to 1%, less than 1%, and unknown for 172 (47%), 94 (26%), and 98 patients (27%), respectively. Median follow-up from pembrolizumab-chemotherapy initiation to data cutoff was 26.2 months. Overall, median pembrolizumab rwToT was 6.5 months (95% confidence interval [CI]: 5.6–7.6), with on-treatment rates of 29.3% and 15.9% at 12 and 24 months, respectively. Median OS was 15.3 months (95% CI: 11.7–18.6), with 12- and 24-month OS rates of 54.9% and 37.3%, respectively. Median OS did not differ with PD-L1 expression: 16.2 months (95% CI: 10.3–20.6) for PD-L1 greater than or equal to 1% and 17.2 months (95% CI: 10.8–20.6) for PD-L1 less than 1%.

Conclusions: For patients with advanced squamous NSCLC and good performance status treated with first-line pembrolizumab-chemotherapy, rwToT and OS are similar to clinical trial findings for treatment duration and OS.

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Introduction

Approximately 20% to 30% of patients with NSCLC have squamous cell carcinoma.[1–3] Relative to those with the more common lung adenocarcinoma, patients with squamous NSCLC are more often male, smokers, and older, with more comorbidities, and overall have a worse prognosis.[2–5] Advanced squamous NSCLC was historically treated with first-line platinum-based doublet chemotherapy, with median overall survival (OS) consistently less than 12 months.[3,5] This led to the search for innovative treatments, such as immune checkpoint inhibitors (ICIs), to improve survival. The approval of ICIs that inhibit the programmed cell death protein 1 pathway has led to recent changes in recommended therapy options in the United States (U.S.): the current category 1 and preferred first-line therapy option for advanced squamous NSCLC in U.S. NSCLC guidelines is pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (pembrolizumab-chemotherapy) (see the National Comprehensive Cancer Network Guidelines for other treatment options).[6]

These treatment recommendations and the October 2018 regulatory approval of this regimen in the U.S. were based on results of the phase 3 clinical trial KEYNOTE-407, in which the median OS was 17.1 months, with a 24-month OS rate of 37.5%, for patients with previously untreated, stage IV squamous NSCLC who received pembrolizumab-chemotherapy.[7,8] The OS benefit of the pembrolizumab-chemotherapy regimen was substantial, regardless of tumor programmed death-ligand 1 (PD-L1) expression level. KEYNOTE-407 had standard trial entry criteria, such as requiring absence of major comorbidities,[7] as is typical for most oncology registration trials. Nevertheless, these eligibility criteria can limit the generalizability of results, as patients in real-world oncology practice tend to be older, with more comorbidities than patients treated in clinical trials.[9–11]

Little information is currently available regarding the real-world effectiveness of first-line pembrolizumab-chemotherapy for patients with advanced squamous NSCLC. The objectives of this retrospective study were to describe the characteristics of patients with advanced squamous NSCLC who were treated with first-line pembrolizumab-chemotherapy and to evaluate OS and their real-world time on treatment (rwToT) with pembrolizumab.

Materials and Methods

Data Source

This study used the nationwide Flatiron Health electronic health record–derived oncology database, which comprises longitudinal, deidentified patient-level structured and unstructured data from U.S. cancer clinics.[12,13] The structured data include laboratory test results and administered drugs, for example, whereas unstructured data, such as radiology reports, pathology reports, and caregiver notes, are curated by means of technology-enabled abstraction, as previously described.[3,14] At the time of the study, the database covered approximately 280 cancer clinics (approximately 800 sites of care) throughout the U.S.. Institutional review board approval of the study protocol was obtained from the WCG Institutional Review Board, with a waiver of informed consent granted for working with deidentified data. The deidentified data are subject to obligations to prevent reidentification and protect patient confidentiality.

Patient Population

We included patients who initiated first-line pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel (henceforth referred to as pembrolizumab-chemotherapy) for treating histologically confirmed, advanced squamous NSCLC from the time of regulatory approval in the U.S. (November 1, 2018) to May 31, 2020. Advanced squamous NSCLC was defined as unresectable stage IIIB, IIIC, IVA, or IVB at presentation or NSCLC diagnosed at an early stage that subsequently developed into recurrent or progressive disease.[3] Eligible patients were 18 years or older at initiation of first-line therapy and had Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Patients who were enrolled in a clinical trial were excluded, as were those lacking recorded structured activity in the database within 90 days after the advanced NSCLC diagnosis. We followed the study cohort until data cutoff on October 31, 2021, hence allowing for a potential minimum of 17 months of theoretical follow-up from first-line therapy initiation to data cutoff.

Study Measures and Statistical Analyses

Descriptive statistics were used to summarize available patient data including demographic and clinical characteristics overall and stratified by PD-L1 expression ($\geq$1%, $<$1%, and unknown). The Charlson comorbidity index score was derived from the listed comorbidities.[15]

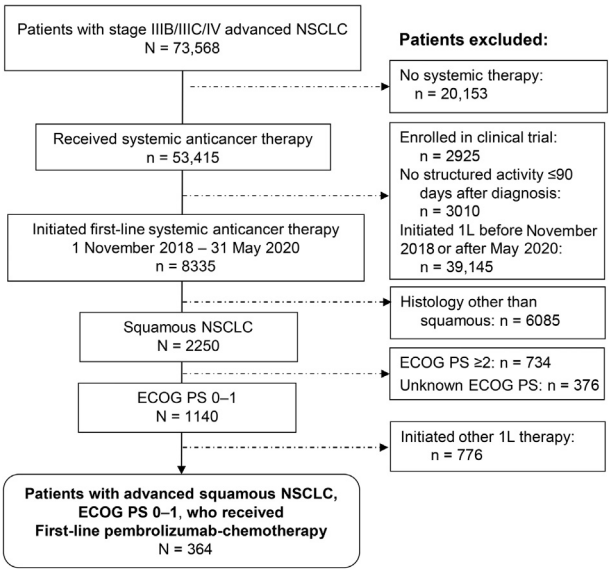

Figure 1. Flow diagram depicting patient selection from the Flatiron Health database. 1L, first line; ECOG PS, Eastern Cooperative Oncology Group performance status.

The Kaplan-Meier method was used to estimate time-to-event outcomes, overall and by PD-L1 expression, including rwToT with first-line pembrolizumab and OS. Lines of therapy were identified using oncologist-defined, rules-based lines of therapy,[3] and Flatiron Health's validated real-world mortality end point was used to determine dates of death.[16–18] Pembrolizumab rwToT was defined from first to last recorded dose, with discontinuation defined at the last pembrolizumab administration date if patients died, initiated second-line therapy, or had a gap in therapy of more than or equal to 120 days. Patients meeting none of these discontinuation criteria were censored at their last pembrolizumab administration date. The median rwToT, 12- and 24-month on-treatment rates, and 12- and 24-month restricted mean rwToT were determined as previously described.[19] For determining OS, the date of death was set according to rules to maintain data deidentification, as summarized in the Supplementary Materials, and patients with no recorded death were censored at the last record of clinical activity in the database before data cutoff.

All patients who met the eligibility criteria were included in the study; therefore, no a priori power analyses were conducted. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

Patients

Of 8335 patients in the database with advanced NSCLC who initiated first-line systemic anticancer therapy during the predefined 19-month period (November 2018–May 2020), 1140 (14%) had squamous NSCLC and presented with ECOG PS of 0 to 1 (Fig. 1). Pembrolizumab-chemotherapy was the most common first-line regimen, administered to 364 of these 1140 patients (32%), followed by carboplatin-paclitaxel (338 patients; 30%) and pembrolizumab monotherapy (138; 12%).

Of the 364 patients who received pembrolizumab-chemotherapy, 266 patients (73%) had tumors with recorded PD-L1 expression, including 172 patients (65%, or 47% of all included patients) with PD-L1 expression greater than or equal to 1% and 94 (35%, or 26% of all) with PD-L1 expression less than 1%; whereas 98 patients (27% of all) had unknown PD-L1 expression. Among those with known PD-L1 immunohistochemistry assay, the 22C3 clone was used most often for PD-L1 determination (Table 1). Most patients were seen at community oncology clinics; only 17 patients overall (5%) were seen at academic centers.

Median patient age was 70 (range: 43–84) years, and patients who were 75 years or older included 56 (33%), 36 (38%), and 29 (30%) in PD-L1 expression greater than or equal to 1%, less than 1%, and unknown cohorts, respectively (Table 1). Two-thirds of patients overall and in each PD-L1 expression cohort were men, and most patients had a history of smoking (≥94% in each cohort). Overall baseline demographic and clinical characteristics are tabulated side by side with those of patients in the pembrolizumab plus chemotherapy group of KEYNOTE-407 in Supplementary Table 1.[7,8]

Follow-Up and rwToT With Pembrolizumab

The median follow-up from initiation of first-line pembrolizumab-chemotherapy to database cutoff (October 31, 2021) was 26.2 months overall (range: 17.1–36.0 mo) and was similar by PD-L1 expression (Table 2).

Patients received a median of nine pembrolizumab doses (range: 1–49 doses), and the median rwToT was 6.5 months (95% confidence interval [CI]: 5.6–7.6), with on-treatment rates of 29.3% at 12 months and 15.9% at 24 months. The pembrolizumab rwToT findings were similar in each PD-L1 expression cohort, as depicted in Table 2 and Figure 2. The median rwToT with pembrolizumab in patients who received paclitaxel was 6.5 months (95% CI: 5.1–7.9) and those who received nab-paclitaxel was 6.7 months (95% CI: 4.6–8.2; Supplementary Table 2).

Of the 364 patients who initiated first-line pembrolizumab-chemotherapy, 108 (30%) continued to second-line therapy and 37 (10%) continued to third-line therapy. Regimens including antiprogrammed cell death

Table 1. Baseline Characteristics of Patients With Advanced Squamous NSCLC Treated With First-Line Pembrolizumab-Chemotherapy, Overall and by PD-L1 Expression

Characteristics	All Patients N = 364	PD-L1 Expression ≥1%[a] n = 172	PD-L1 Expression <1% n = 94	PD-L1 Expression Unknown n = 98
Age, median (range), y	70 (43-84)	70 (43-84)	72 (52-84)	69 (50-84)
Age group, y				
<75	243 (66.8)	116 (67.4)	58 (61.7)	69 (70.4)
≥75	121 (33.2)	56 (32.6)	36 (38.3)	29 (29.6)
Sex, male	243 (66.8)	115 (66.9)	62 (66.0)	66 (67.3)
Race[b]				
White	260 (78.5)	119 (76.3)	68 (80.0)	73 (81.1)
Black or African American	28 (8.5)	15 (9.6)	6 (7.1)	7 (7.8)
Other	43 (13.0)	22 (14.1)	11 (12.9)	10 (11.1)
Unknown	33	16	9	8
Smoking status				
Positive history of smoking	353 (97.0)	168 (97.7)	88 (93.6)	97 (99.0)
Practice type				
Academic or both	17 (4.7)	8 (4.7)	9 (9.6)	0
Community	347 (95.3)	164 (95.3)	85 (90.4)	98 (100)
ECOG PS				
0	133 (36.5)	51 (29.7)	41 (43.6)	41 (41.8)
1	231 (63.5)	121 (70.3)	53 (56.4)	57 (58.2)
Charlson comorbidity index				
Mean (SD)	5.0 (3.2)	5.0 (3.1)	5.0 (3.4)	4.8 (3.1)
Median (range)	3 (0-14)	3 (2-14)	3 (2-14)	3 (0-12)
Brain metastasis[c]	16 (4.4)	7 (4.1)	4 (4.3)	5 (5.1)
Advanced stage at initial diagnosis[b,d]	271 (76.3)	134 (78.4)	65 (72.2)	72 (76.6)
Stage IV at initial diagnosis	245 (69.0)	119 (69.6)	60 (66.7)	66 (70.2)
IHC clone for PD-L1 determination				
22C3[e]	231 (63.5)	147 (85.5)	75 (79.8)	9 (9.2)
Other	28 (7.7)	14 (8.1)	9 (9.6)	5 (5.1)
Unknown, missing, or not documented	105 (28.8)	11 (6.4)	10 (10.6)	84 (85.7)
Taxane chemotherapy				
Paclitaxel	197 (54.1)	97 (56.4)	48 (51.1)	52 (53.1)
Nab-paclitaxel	167 (45.9)	75 (43.6)	46 (48.9)	46 (46.9)

Note: Data are n (%) unless otherwise noted. Percentages may not add up to 100 because of rounding.
[a]Patients with PD-L1 expression of greater than or equal to 1% included 48 patients (28%) with PD-L1 greater than or equal to 50% and 124 (72%) with PD-L1 expression of 1% to 49%.
[b]Percentages for race and stage at initial diagnosis represent the percentages of patients with available data.
[c]It was not possible to identify whether patients had active brain metastasis in this observational study.
[d]Advanced stage at initial diagnosis included stages IIIB, IIIC, and IV. (Nine patients had no recorded stage at diagnosis.)
[e]Of the 22C3 IHC assays, 219 of 231 (95%) used the PD-L1 IHC 22C3 pharmDx, pembrolizumab companion diagnostic assay.
ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; PD-L1, programmed death-ligand 1.

protein 1 or anti-PD-L1 agents were administered most often in the second-line setting (34 patients; 32%), followed by regimens containing platinum-based chemotherapy (23; 21%), single-agent chemotherapy (23; 21%), and antivascular endothelial growth factor therapy (22; 20%; details in Supplementary Table 3).

Survival Outcomes

At the end of follow-up, 221 patients had died (60.7%) and median OS was 15.3 months (95% CI: 11.7–18.6; Fig. 3). The OS rate was 54.9% at 12 months and 37.3% at 24 months. Median OS was 16.2 months, 17.2 months, and 12.4 months in PD-L1 expression greater than or equal to 1%, less than 1%, and unknown cohorts, respectively, and 12-month OS rates were 56.0%, 57.3%, and 50.7%, respectively (Fig. 3).

Follow-up time and key outcome measures for all patients are tabulated side by side with those of patients in the pembrolizumab plus chemotherapy group of KEYNOTE-407 in Supplementary Table 4.[8]

Table 2. Follow-Up Time and rwToT With Pembrolizumab for Patients With Advanced Squamous NSCLC Treated With First-Line Pembrolizumab-Chemotherapy, Overall and by PD-L1 Expression

Characteristics	All Patients N = 364	PD-L1 Expression ≥1% n = 172	PD-L1 Expression <1% n = 94	PD-L1 Expression Unknown n = 98
Theoretical follow-up, median (range), mo[a]	26.2 (17.1-36.0)	26.0 (17.1-35.9)	27.0 (17.1-35.5)	25.8 (17.1-36.0)
Patient follow-up, median (range), mo[a]	17.1 (<0.1-35.8)	17.1 (<0.1-35.8)	17.3 (<0.1-35.0)	14.1 (<0.1-35.8)
Pembrolizumab doses, median (range)	9 (1-49)	9 (1-47)	9 (1-49)	9 (1-49)
Discontinued pembrolizumab, n (%)	289 (79.4)	136 (79.1)	74 (78.7)	79 (80.6)
rwToT, median (95% CI), mo	6.5 (5.6-7.6)	6.9 (5.3-8.3)	5.8 (4.6-8.3)	6.3 (4.2-8.2)
On-treatment rate, % (95% CI)[b]				
At 12 mo	29.3 (24.6-34.2)	28.6 (21.9-35.7)	31.5 (22.2-41.2)	28.6 (19.9-37.9)
At 24 mo	15.9 (11.8-20.6)	16.3 (10.6-23.2)	15.8 (8.4-25.2)	15.3 (7.9-25.1)
Restricted mean rwToT (95% CI), mo				
Restricted to 12 mo	6.7 (6.3-7.2)	6.8 (6.2-7.5)	6.8 (6.0-7.7)	6.5 (5.6-7.4)
Restricted to 24 mo	9.6 (8.7-10.5) [Weibull]	9.7 (8.5-11.1) [Weibull]	9.8 (8.3-11.7) [log logistic]	9.1 (7.5-11.0) [Weibull]

[a]Theoretical follow-up was defined as the duration of follow-up from first-line therapy initiation to database cutoff (October 31, 2021). Patient follow-up was defined as time from first-line therapy initiation to the date of death or data cutoff, whichever occurred first.
[b]On-treatment rates were based on Kaplan-Meier estimates.
CI, confidence interval; mo, month; PD-L1, programmed death-ligand 1; rwToT, real-world time on treatment.

Discussion

The findings of this retrospective observational study conducted in the U.S. suggest real-world benefits of first-line pembrolizumab-chemotherapy for patients with advanced squamous NSCLC and good performance status, across PD-L1 expression strata. The median rwToT with pembrolizumab was 6.5 months overall and was similar for patients with PD-L1 expression greater

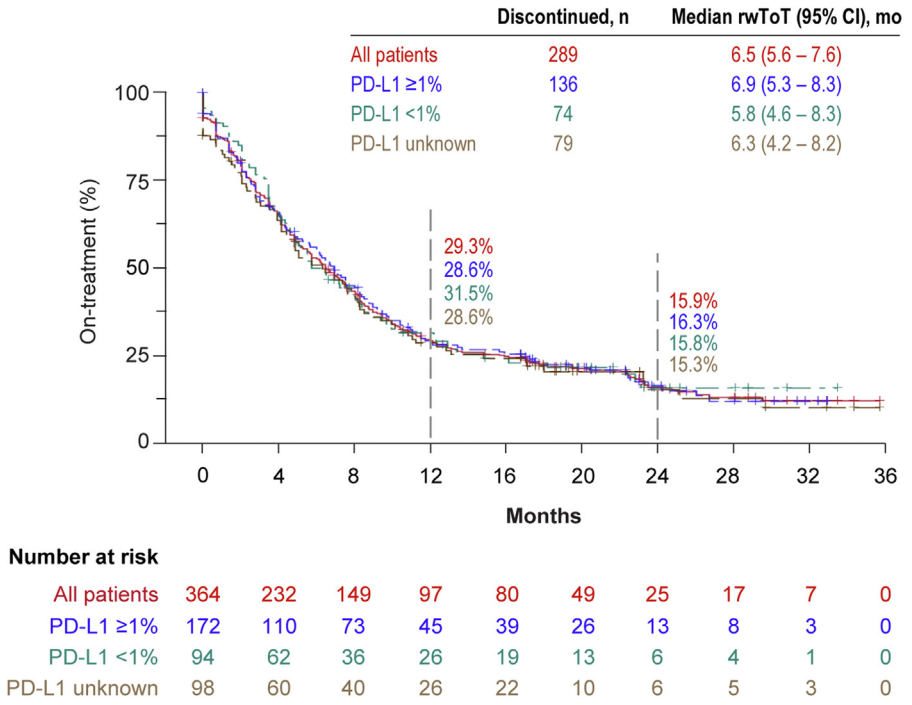

Figure 2. Real-world time on treatment with pembrolizumab for patients with advanced squamous NSCLC treated with first-line pembrolizumab-chemotherapy, overall and by PD-L1 expression. CI, confidence interval; mo, month; PD-L1, programmed death-ligand 1; rwToT, real-world time on treatment.

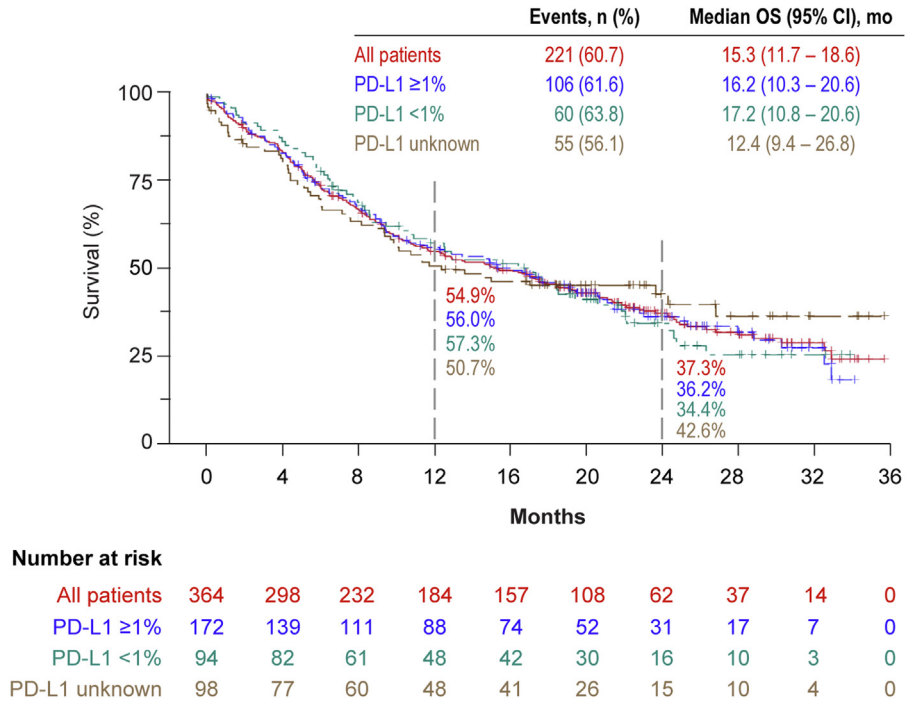

Figure 3. Overall survival of patients with advanced squamous NSCLC treated with first-line pembrolizumab-chemotherapy, overall and by PD-L1 expression. CI, confidence interval; mo, months; OS, overall survival; PD-L1, programmed death-ligand 1.

than or equal to 1% versus less than 1% (6.9 versus 5.8 mo, respectively). Regardless of PD-L1 expression, a similar percentage of patients (28.6% and 31.5%) remained on pembrolizumab at 12 months. Approximately one in six patients remained on pembrolizumab at 24 months (16.3% and 15.8%). For continuously administered therapies such as pembrolizumab, the rwToT end point, also known as time to treatment discontinuation, has been highly correlated with progression-free survival at the patient level in clinical trials and moderately to highly correlated with OS in prior real-world studies.[20–22] Median OS in this study was 15.3 months overall, and we observed that survival was similar in the two PD-L1 cohorts, with median OS of 16.2 versus 17.2 months, respectively, and OS rate at 12 months of 56.0% in the PD-L1 expression greater than or equal to 1% cohort and 57.3% in the PD-L1 less than 1% cohort.

Our findings for patients with advanced squamous NSCLC and good performance status were consistent with those for patients in the pembrolizumab plus chemotherapy group of KEYNOTE-407, in which median duration of pembrolizumab therapy was 7.1 months[8] (6.5 mo in the present study). Median OS was 17.1 months (95% CI: 14.4–19.9) in KEYNOTE-407 with 12- and 24-month OS rates of 64.7% and 37.5%, respectively, whereas median OS was 15.3 months (95% CI: 11.7–18.6) in the present study, with 12- and 24-month OS rates of 54.9% and 37.3%, respectively (Supplementary Table 4).[8]

The patients in our study had good performance status; however, they differed in other respects from the clinical trial patients (Supplementary Table 1).[7,8] The patients in our study were older than those in KEYNOTE-407 (median, 70 y versus 65 y). This highlights the corporeality of patients being treated in the real-world setting. Despite the older age of patients in our study, the results did not vary from KEYNOTE-407, signifying the usefulness of pembrolizumab plus chemotherapy in older patients. In addition, the median Charlson comorbidity index was 5 and ranged up to 14, indicating that many of these patients had comorbidities and some had multiple comorbidities. Furthermore, our real-world population included more women (33% versus 21% in KEYNOTE-407); such differences between real-world and clinical trial populations have also been reported in prior observational studies.[9,14,19] Nevertheless, the percentages with PD-L1–expressing tumors were similar: of patients with known PD-L1, 65% had PD-L1 greater than or equal to 1%, and in the pembrolizumab plus chemotherapy group from KEYNOTE-407, 63% of patients had PD-L1 greater than or equal to 1%.

Regulatory approvals of ICIs for NSCLC, initially for previously treated NSCLC, have occurred only within the past 6 years, and we found a limited number of studies evaluating real-world outcomes with first-line ICI-

chemotherapy combinations for advanced squamous NSCLC. In a study that also used the Flatiron Health database but was not limited to patients with good performance status, Waterhouse et al.[23] reported Kaplan-Meier duration of therapy of 4.3 months and median OS of 11.3 months (95% CI: 9.8–12.8) for 814 patients with advanced squamous NSCLC who received combination therapy with an ICI and chemotherapy, 94% of whom received pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel. Although patient demographic characteristics resembled those in the present study, because patients with ECOG PS greater than or equal to 2 and unknown ECOG PS were included, the clinical characteristics differed. Moreover, median patient follow-up from first-line therapy initiation to last date of follow-up or data cutoff was only 6.6 months (versus 17.1 mo in our study), making it difficult to compare the two studies. In another study of treatment patterns for patients in the Flatiron Health database with stage IV NSCLC who initiated first-line systemic therapy during a timeline similar to that of the present study (August 2018 to December 2019), 447 of 911 patients (49%) with squamous NSCLC in that study received combination ICI-chemotherapy; however, outcomes were not reported.[24] Other recent observational studies included too few patients with advanced squamous NSCLC receiving ICI-chemotherapy to warrant discussion in the context of the present study.[25–29]

Our study included a well-characterized, large patient population of more than 350 patients selected from a well-regarded database that is frequently used for oncology research.[3,12–14] Another strength of the study is the relatively long follow-up. The study design allowed for a minimum of 17 months and a median of 26.2 months theoretical follow-up until data cutoff, and median patient follow-up from first-line therapy initiation to death or data cutoff was 17.1 months. The study drew on data originating from patients receiving care at real-world oncology settings, most being community oncology clinics, where most people with cancer are treated.

Because 95% of patients were treated exclusively at community oncology clinics, our findings may not be generalizable to patients treated in academic settings, nor to those treated outside the Flatiron Health network. Another study limitation is that data for some variables were missing, including PD-L1 expression for approximately one-quarter of patients. In addition, otherwise eligible patients with unknown ECOG PS were excluded from the study, raising the possibility of selection bias. Finally, these findings are purely descriptive, and causality should not be inferred.

Continued study with longer follow-up of larger real-world patient populations with advanced squamous NSCLC treated with first-line pembrolizumab plus chemotherapy will be of interest. Subgroups of interest for future studies include patients with ECOG PS of 2, older patients (such as those $\geq$75 y old), and patients with multiple comorbidities.

In conclusion, for patients with advanced squamous NSCLC with good performance status treated with first-line pembrolizumab-chemotherapy at U.S. oncology clinics, rwToT and OS are similar to treatment duration and OS reported in KEYNOTE-407.[8] Approximately one in six patients (16%) remained on pembrolizumab at 2 years, suggesting long-term treatment effect, and survival outcomes were consistent regardless of PD-L1 expression, with benefit evident for patients with PD-L1 expression less than 1%, as previously reported in KEYNOTE-407.[8,30] Our findings suggest real-world benefits of first-line pembrolizumab plus chemotherapy for advanced squamous NSCLC regardless of PD-L1 expression for these patients with good performance status.

CRediT Authorship Contribution Statement

Stephen V. Liu: Validation, Methodology, Writing—review and editing, Visualization.

Pragya Rai: Conceptualization, Methodology, Investigation, Resources, Writing—original draft, Writing—review and editing, Project administration, Supervision, Funding acquisition.

Dong Wang: Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Project administration, Writing—review and editing, Visualization.

Xiaohan Hu: Conceptualization, Methodology, Investigation, Resources, Writing—review and editing, Visualization.

Paul Otto Schwarzenberger: Validation, Methodology, Writing—review and editing, Visualization.

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Data Sharing Statement

The data that support the findings of this study have been originated by Flatiron Health, Inc. These deidentified data may be made available on request and are subject to a license agreement with Flatiron Health; interested researchers should contact DataAccess@flatiron.com to determine licensing terms.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at 10.1016/j.jtocrr.2022.100444.

References

1. de Castro J, Tagliaferri P, de Lima VCC, et al. Systemic therapy treatment patterns in patients with advanced non-small cell lung cancer (NSCLC): PIvOTAL study. *Eur J Cancer Care (Engl)*. 2017;26:e12734.
2. Socinski MA, Obasaju C, Gandara D, et al. Clinicopathologic features of advanced squamous NSCLC. *J Thorac Oncol*. 2016;11:1411–1422.
3. Abernethy AP, Arunachalam A, Burke T, et al. Real-world first-line treatment and overall survival in non-small cell lung cancer without known EGFR mutations or ALK rearrangements in US community oncology setting. *PLoS One*. 2017;12:e0178420.
4. Subramanian J, Morgensztern D, Goodgame B, et al. Distinctive characteristics of non-small cell lung cancer (NSCLC) in the young: a surveillance, epidemiology, and end results (SEER) analysis. *J Thorac Oncol*. 2010;5:23–28.
5. Socinski MA, Obasaju C, Gandara D, et al. Current and emergent therapy options for advanced squamous cell lung cancer. *J Thorac Oncol*. 2018;13:165–183.
6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for non-small cell lung cancer, V3. https://www.nccn.org/; 2022. Accessed May 6, 2022. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.3.2022.
7. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040–2051.
8. Paz-Ares L, Vicente D, Tafreshi A, et al. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: protocol-specified final analysis of KEYNOTE-407. *J Thorac Oncol*. 2020;15:1657–1669.
9. Sedrak MS, Freedman RA, Cohen HJ, et al. Older adult participation in cancer clinical trials: a systematic review of barriers and interventions. *CA Cancer J Clin*. 2021;71:78–92.
10. Abi Jaoude J, Kouzy R, Mainwaring W, et al. Performance status restriction in phase III cancer clinical trials. *J Natl Compr Canc Netw*. 2020;18:1322–1326.
11. Unger JM, Hershman DL, Fleury ME, Vaidya R. Association of patient comorbid conditions with cancer clinical trial participation [published correction appears in JAMA Oncol. 2019;5:436]. *JAMA Oncol*. 2019;5:326–333.
12. Flatiron Health. About us. https://flatiron.com/about-us/. Accessed November 7, 2022.
13. Flatiron Health. Flatiron Health database. https://flatiron.com/real-world-evidence/. Accessed November 7, 2022.
14. Khozin S, Abernethy AP, Nussbaum NC, et al. Characteristics of real-world metastatic non-small cell lung cancer patients treated with nivolumab and pembrolizumab during the year following approval. *Oncologist*. 2018;23:328–336.
15. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43:1130–1139.
16. Curtis MD, Griffith SD, Tucker M, et al. Development and validation of a high-quality composite real-world mortality endpoint. *Health Serv Res*. 2018;53:4460–4476.
17. Carrigan G, Whipple S, Taylor MD, et al. An evaluation of the impact of missing deaths on overall survival analyses of advanced non-small cell lung cancer patients conducted in an electronic health records database. *Pharmacoepidemiol Drug Saf*. 2019;28:572–581.
18. Zhang Q, Gossai A, Monroe S, Nussbaum NC, Parrinello CM. Validation analysis of a composite real-world mortality endpoint for patients with cancer in the United States. *Health Serv Res*. 2021;56:1281–1287.
19. Velcheti V, Chandwani S, Chen X, Pietanza MC, Burke T. First-line pembrolizumab monotherapy for metastatic PD-L1-positive NSCLC: real-world analysis of time on treatment. *Immunotherapy*. 2019;11:889–901.
20. Blumenthal GM, Gong Y, Kehl K, et al. Analysis of time-to-treatment discontinuation of targeted therapy, immunotherapy, and chemotherapy in clinical trials of patients with non-small-cell lung cancer. *Ann Oncol*. 2019;30:830–838.
21. Khozin S, Miksad RA, Adami J, et al. Real-world progression, treatment, and survival outcomes during rapid adoption of immunotherapy for advanced non-small cell lung cancer. *Cancer*. 2019;125:4019–4032.
22. Stewart M, Norden AD, Dreyer N, et al. An exploratory analysis of real-world end points for assessing outcomes among immunotherapy-treated patients with advanced non-small-cell lung cancer. *JCO Clin Cancer Inform*. 2019;3:1–15.
23. Waterhouse D, Lam J, Betts KA, et al. Real-world outcomes of immunotherapy-based regimens in first-line advanced non-small cell lung cancer. *Lung Cancer*. 2021;156:41–49.
24. Stenehjem D, Lubinga S, Betts KA, et al. Treatment patterns in patients with metastatic non-small-cell lung

cancer in the era of immunotherapy. *Future Oncol*. 2021;17:2940–2949.
25. Spini A, Gini R, Rosellini P, et al. First-line pharmacotherapies and survival among patients diagnosed with non-resectable NSCLC: a real-life setting study with gender prospective. *Cancers (Basel)*. 2021;13:6129.
26. Carroll R, Bortolini M, Calleja A, et al. Trends in treatment patterns and survival outcomes in advanced non-small cell lung cancer: a Canadian population-based real-world analysis. *BMC Cancer*. 2022;22:255.
27. Veraldi M, Esposito S, Naturale MD, et al. Real-world data on patients with metastatic non-small-cell lung cancer treated with checkpoint inhibitors in an Italian Teaching Hospital in 2015–2018. *J Oncol Pharm Pract*. 2021;27:877–886.
28. Nadler E, Arondekar B, Aguilar KM, et al. Treatment patterns and clinical outcomes in patients with advanced non-small cell lung cancer initiating first-line treatment in the US community oncology setting: a real-world retrospective observational study. *J Cancer Res Clin Oncol*. 2021;147:671–690.
29. Mouritzen MT, Carus A, Ladekarl M, et al. Nationwide survival benefit after implementation of first-line immunotherapy for patients with advanced NSCLC—real world efficacy. *Cancers (Basel)*. 2021;13:4846.
30. Borghaei H, Langer CJ, Paz-Ares L, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone in patients with advanced non-small cell lung cancer without tumor PD-L1 expression: a pooled analysis of 3 randomized controlled trials. *Cancer*. 2020;126:4867–4877.