ORIGINAL ARTICLE

Real-World Immunotherapy Use and Effectiveness in Advanced NSCLC With Programmed Death-Ligand 1 Greater Than or Equal to 50% and Greater Than or Equal to 90%

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Received 11 October 2023; revised 2 November 2023; accepted 8 November 2023
Available online - 14 November 2023

ABSTRACT

Background: Immunotherapy has vastly changed the treatment landscape for patients with advanced NSCLC. With high programmed death-ligand 1 (PD-L1) expression (tumor proportion score ≥50%), options include programmed cell death protein 1 or PD-L1 inhibitor with or without chemotherapy. A cut-point of greater than or equal to 50% defines PD-L1–high, but a more precise PD-L1 tumor proportion score may be an important predictor of outcomes.

Methods: We reviewed all patients with PD-L1–high NSCLC who received pembrolizumab from June 2019 to June 2021. Demographic, diagnosis, treatment, and outcomes data were collected retrospectively. The primary end point was a descriptive analysis of pembrolizumab prescribing patterns. Secondary end points included overall survival (OS) by treatment choice and absolute PD-L1 expression.

Results: Overall, 132 patients received pembrolizumab; 124 (94%) as monotherapy, and 8 (6%) with chemotherapy. Baseline characteristics include the following: (1) median age 70 years (50–89); (2) 55% men; (3) 79% Eastern Cooperative Oncology Group performance status 0 to 1; and (4) 96% current or former smokers. There were 39% who have PD-L1 greater than or equal to 90% versus 61% with PD-L1 of 50% to 89%. The median OS in the overall population was 14.4 months. The median OS in the pembrolizumab monotherapy cohort and combination cohort were 13.6 months and 16.6 months, respectively ($p = 0.67$). Within the monotherapy cohort, the median OS was longer for PD-L1 greater than or equal to 90% (19.8 mo) versus PD-L1 50% to 89% (11.9 mo, $p = 0.039$). The 24-month OS was 27.8% among patients with PD-L1 50% to 89% and 47.4% among patients with PD-L1 greater than or equal to 90%.

Conclusions: Most patients with advanced PD-L1–high NSCLC received pembrolizumab monotherapy, among whom OS was strongly correlated with PD-L1 expression, with PD-L1 greater than or equal to 90% of patients experiencing substantially longer survival. PD-L1 expression level could be an important determinant in immunotherapy prescribing patterns and a predictor of success in advanced NSCLC.

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Disclosure: Dr. Wheatley-Price has received personal fees in the past 24 months for advisory boards or speaking honoraria from the following: Merck, AstraZeneca, Roche, Bristol-Myers Squibb, Eli Lilly, Novartis, Sanofi, Pfizer, Guardant, Janssen, and Bayer. Dr. Moore has received personal fees from speaking honoraria from AstraZeneca and Bristol-Myers Squibb. The remaining authors declare no conflict of interest.

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Cite this article as: Jackson A, Chang N, Akurang D, Wheatley-Price P, Moore S. Real-world immunotherapy use and effectiveness in advanced NSCLC with programmed death-ligand 1 greater than or equal to 50% and greater than or equal to 90%. *JTO Clin Res Rep*. 2023;4:100601.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2023.100601

Keywords: Pembrolizumab; NSCLC; PD-L1; Tumor proportion score; Overall survival

Introduction

Lung cancer is the leading cause of cancer death among Canadians and the most frequently diagnosed of all cancers.[1] The most common type of lung cancer is NSCLC,1 which accounts for approximately 85% of lung cancer diagnoses in Canada and nearly half of all NSCLC cases are diagnosed at stage IV.[2,3] Because of both the aggressiveness of the cancer and late diagnosis, the 5-year survival rate for lung cancer remains low at 22%.[4]

In the past few years, immunotherapy has drastically changed the treatment landscape of advanced NSCLC.[5,6] The most typically used immunotherapy agent for the treatment of advanced NSCLC is pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor that functions by blocking the binding of programmed death-ligand 1 (PD-L1) on tumor cells to its receptor, PD-1, on immune cells.[7] The choice of administering immunotherapy alone or in combination with chemotherapy is largely driven by PD-L1 tumor expression, with PD-L1 tumor proportion score (TPS) greater than or equal to 50% taken as the cutoff value to define PD-L1–high disease.

Previous research has already reported on the superiority of pembrolizumab over chemotherapy in patients with NSCLC having PD-L1 expression greater than or equal to 50%.[8] Other studies have reported that the combination of pembrolizumab plus chemotherapy is superior to chemotherapy in metastatic NSCLC, regardless of PD-L1 levels.[9,10] However, no study to date has directly compared the efficacy of pembrolizumab monotherapy to that of combination therapy with pembrolizumab plus chemotherapy. There are no definitive guidelines to advise on the decision to treat patients with PD-L1 greater than or equal to 50% with either pembrolizumab monotherapy or combination therapy. However, more precise PD-L1 TPS (i.e., given in 10% increments), rather than the broad greater than or equal to 50% cutoff, is being considered an increasingly important factor in decision-making, as studies have identified that patients with very high PD-L1 expression levels ($\geq$ 90%) have better responses to single-agent immunotherapy.[11,12] Given the adverse effects of chemotherapy and the impact on quality of life, it is important to elucidate whether immunotherapy alone is as effective as combination therapy in patients with PD-L1–positive NSCLC.

We sought to review all patients at our institution with PD-L1–high NSCLC who received pembrolizumab. The objectives were to characterize factors influencing immunotherapy prescribing patterns and to compare treatment outcomes on the basis of PD-L1 TPS levels among those who were treated with pembrolizumab monotherapy compared with those treated with combination therapy.

Materials and Methods

With local research ethics board approval, we completed a retrospective review of all patients with lung cancer at the Ottawa Hospital Cancer Centre who received treatment with pembrolizumab between June 1, 2019 and June 1, 2021. Eligible patients were required to have histologically confirmed NSCLC, a PD-L1 TPS greater than or equal to 50% (using 22C3 antibody), and to have received pembrolizumab as part of their first-line treatment for metastatic or advanced NSCLC. Patients were identified through the institutional oncology pharmacy records. Cases were then filtered to exclude those not fulfilling the eligibility criteria. Data on patient demographics, diagnostic information, treatment regimens, and outcomes were collected using a retrospective review of hospital electronic medical records. PD-L1 TPS were categorized as 50% to 89%, greater than or equal to 90%, and greater than or equal to 50% not otherwise specified.

Primary end points included a descriptive analysis of prescribing patterns of pembrolizumab among patients with NSCLC who have PD-L1 expression greater than or equal to 50% and the proportion of patients who received pembrolizumab monotherapy to those who received a combination regimen of pembrolizumab and chemotherapy. Secondary end points included factors associated with the decision to prescribe pembrolizumab either alone or in combination, including PD-L1 TPS, stage at diagnosis, pathologic subtype, and comorbidities, outcomes of treatment including overall survival (OS), and the impact of PD-L1 TPS on treatment choices and outcomes.

Statistical analysis was performed using Statistical Package for the Social Sciences version 28. Known prognostic factors were compared between cohorts using the chi-square test or Fisher's exact test in which appropriate (categorical variables), and the Mann-Whitney test (continuous variables). OS was calculated from the date of diagnosis of advanced or metastatic disease. Survival curves were compared between cohorts using a log-rank test.

Results

During the study period, 240 patients with lung cancer at the Ottawa Hospital Cancer Centre received pembrolizumab as part of their treatment. Of these, 132

Table 1. Baseline Characteristics of the Study Population and Monotherapy and Combination Therapy Subgroups

Baseline Characteristics	All patients (N = 132)	%	Combination Therapy (n = 8)	%	Monotherapy (n = 124)	%
Median age at diagnosis (y, range)	70 (50-89)		69 (57-75)		70 (50-89)	
Sex						
Male	72	54.5	2	25.0	70	56.5
Female	60	45.5	6	75.0	54	43.5
Tobacco Exposure						
Never	5	3.8	1	12.5	4	3.2
Minimal (≤10 pack years)	3	2.3	0	0	3	2.4
Former (>10 pack years)	71	53.8	7	87.5	64	51.6
Current	53	40.2	0	0	53	42.7
Median smoking pack years (y, range)	40 (0-180)		31.5 (0-180)		40 (0-150)	
ECOG PS at diagnosis						
0-1	104	78.8	8	100	96	77.4
≥2	28	21.2	0		28	22.6
Median CCI at diagnosis (y, range)	9 (4-14)		9.5 (7-11)		9 (4-14)	
Histologic Type						
Adenocarcinoma	101	76.5	6	75.0	95	76.6
Squamous cell carcinoma	27	20.5	2	25.0	25	20.2
Large cell carcinoma	1	0.75	0	0	1	0.8
NSCLC NOS	2	1.5	0	0	2	1.6
Sarcomatoid carcinoma	1	0.75	0	0	1	0.8
PD-L1 TPS						
50-59%	14	10.6	2	25.0	12	9.7
60-69%	14	10.6	2	25.0	12	9.7
70-79%	20	15.1	1	12.5	19	15.3
80-89%	24	18.2	0	0	24	19.4
90-100%	52	39.4	3	37.5	49	39.5
PD-L1 TPS not specified	8	6.1	0	0	8	6.4
Stage at Initial Diagnosis						
I	8	6.1	1	12.5	7	5.6
II	9	6.8	0	0	9	7.3
III	15	11.4	0	0	15	12.1
IV	100	75.8	7	87.5	93	75.0
KRAS Mutation Status						
G12C	24	18.2	1	12.5	23	18.5
Non-G12C	18	13.6	2	25.0	16	12.9
None	31	23.5	3	37.5	28	22.6
Not done	59	44.7	2	25.0	57	46.0
Brain Metastases						
Yes	39	29.5	2	25.0	37	29.8
No	91	68.9	6	75.0	85	68.5
Unknown	2	1.5	0	0	2	1.6
Liver Metastases						
Yes	20	15.2	1	12.75	19	15.3
No	112	84.8	7	87.5	105	84.7

ECOG PS, Eastern Cooperative Oncology Group performance status; CCI, Charlson Comorbidity Index; NOS, not otherwise specified; TPS, tumor proportion score; PD-L1, programmed death-ligand 1.

had histologically confirmed NSCLC with a PD-L1 TPS greater than or equal to 50% which formed our final study population. The baseline characteristics of our study population are described in Table 1. PD-L1 TPS was available for all but eight (6.1%) patients in the study; 52 patients (39.4%) had PD-L1 expression greater than or equal to 90% and the remaining 80 (60.6%) had an expression level between 50% and 89%.

Treatments Details

There were 124 patients (93.9%) who received pembrolizumab alone, whereas eight (6.1%) received a combination of pembrolizumab and platinum-based chemotherapy. Information on the baseline characteristics of these subgroups is summarized in Table 1.

The median number of pembrolizumab cycles completed by the patients in our study at the time of

data collection was six (range: 1 to 36). Of the 107 patients in our study who discontinued pembrolizumab treatment at some point, 26 went on to second-line therapy. The median number of pembrolizumab cycles completed in the combination therapy subgroup at the time of data collection was 17 (range: 1 to 35). Although two patients completed a full 2-year treatment cycle, the remaining six patients discontinued pembrolizumab at some point during their treatment. Table 2 highlights treatment characteristics and outcomes for the patients in our study.

Survival Analysis

The median OS for patients in our study was 14.4 months (95% confidence interval [CI]: 10.4–18.5). There was no marked difference in OS ($p = 0.674$) among the 124 patients who received pembrolizumab monotherapy (median OS 13.6 mo, 95% CI: 9.1–17.6) compared with those who received a combination of pembrolizumab and chemotherapy (median OS 16.6 months, 95% CI: 15.6–17.6). Figure 1*A* and *B* illustrates the survival of the different treatment groups.

For the 124 patients on pembrolizumab monotherapy, the median OS was determined on the basis of PD-L1 expression. The median OS was significantly longer for PD-L1 greater than or equal to 90% at 19.8 months, compared with 11.9 months for PD-L1 50% to 89% ($p = 0.039$). The 12-month, 24-month, and 36-month OS for PD-L1 greater than or equal to 90% was 56.5%, 47.4%, and 44.9% respectively, whereas the same for PD-L1 50% to 89% was 49.4%, 27.8%, and 22.8%. Additional details on the survival in the pembrolizumab monotherapy group on the basis of PD-L1 expression can be found in Figure 2.

Univariate analysis and multivariable modeling were performed to evaluate the impact of potential prognostic factors on survival outcomes for patients treated with pembrolizumab monotherapy. Because of the small number of patients treated with combination pembrolizumab plus chemotherapy, these patients were excluded from the analysis. Results are presented in Table 3. PD-L1 50% to 89% was associated with an increased risk of death compared with PD-L1 greater than or equal to 90% (hazard ratio [HR] = 1.64, 95% CI: 1.03–2.61), and this remained significant in a multivariable model that included age, sex, tobacco exposure, Eastern Cooperative Oncology Group performance status (ECOG PS), and presence of liver and brain metastases (HR = 1.66, 95% CI: 1.01–2.74).

Discussion

In this institutional review of patients with advanced PD-L1–high NSCLC who received pembrolizumab, we predictably found that pembrolizumab monotherapy is the dominant treatment regimen prescribed, as opposed to combination treatment with chemotherapy. We observed no marked difference in OS between those who received pembrolizumab monotherapy compared with

Table 2. Treatments and Outcomes of the Study Population and Monotherapy and Combination Therapy Groups

Treatment/Outcome Variable	All Patients (N = 132)	%	Combination Therapy (n = 8)	%	Monotherapy (n = 124)	%
Median number of pembrolizumab cycles (y, range)	6 (1-36)		17 (1-35)		6 (1-36)	
Pembrolizumab treatment status						
Completed 2 y treatment	24	18.2	2	25.0	22	17.7
Ongoing	1	0.8	0	0	1	0.8
Discontinued	107	81.1	6	75.0	101	81.5
Reasons for discontinuation	**n = 107**		**n = 6**		**N = 101**	
Death	18	16.8	0	0	18	17.8
Moved or lost to follow-up	2	1.9	0	0	2	2.0
Patient choice	5	4.7	1	16.7	4	4.0
Progression	57	53.3	3	50.0	54	53.5
Toxicity	19	17.8	1	16.7	18	17.8
Other	6	5.6	1	16.7	5	5.0
Second-line therapy						
None	106	80.3	5	62.5	101	81.5
Chemotherapy	22	16.7	2	25.0	20	16.1
Targeted therapy	3	2.3	1	12.5	2	1.6
Other (pembrolizumab rechallenge)	1	0.8	0	0	1	0.8
Vital status						
Alive	43	32.6	3	37.5	40	32.3
Dead	89	67.4	5	62.5	84	67.7

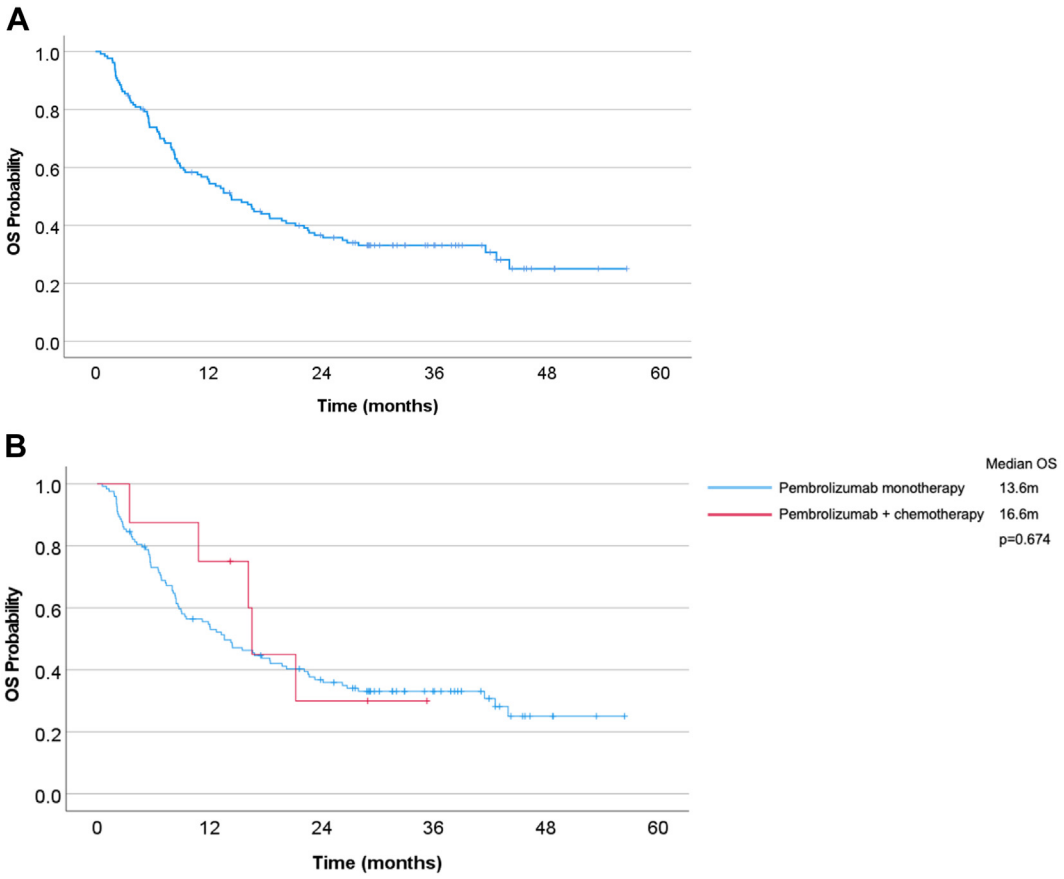

Figure 1. (*A*) OS (mo) for all patients in the study (n = 132). (*B*) OS (mo) for patients who received pembrolizumab monotherapy (n = 124) versus those who received pembrolizumab and chemotherapy combination treatment (n = 8). OS, overall survival.

combination therapy, though the comparison was limited by small numbers in the combination cohort.

The most substantial finding of our study was that the median OS for patients who received pembrolizumab monotherapy was consistently higher in those with PD-L1 greater than or equal to 90% than those with PD-L1 50% to 89%, both when reporting median OS and landmark survival analyses at 12, 24, and 36 months. The exact impact of PD-L1 expression on outcomes in advanced NSCLC has not been well established. However, PD-L1 expression levels have been identified as a potential predictor of treatment

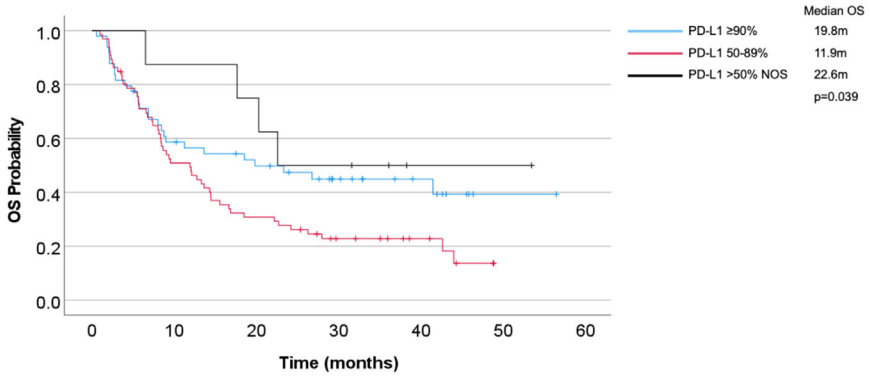

Figure 2. OS (mo) for patients who received pembrolizumab monotherapy (n = 124) on the basis of the PD-L1 category. PD-L1 greater than or equal to 90% (n = 49), PD-L1 50% to 89% (n = 67), PD-L1 greater than 50% NOS (n = 8). OS, overall survival; PD-L1, programmed death-ligand 1; NOS, not otherwise specified.

Table 3. Prognostic Factors for Pembrolizumab Monotherapy Group (N = 124)

Prognostic Factor	No. of patients (N = 124)	UVA HR (95% CI)	MVA HR (95% CI)
PD-L1 category			
≥90%	49	Ref	Ref
50%-89%	67	1.64 (1.03-2.61)	1.66 (1.01-2.74)
>50% NOS	8	0.67 (0.23-1.91)	0.67 (0.23-1.96)
Sex			
Male	70	Ref	Ref
Female	54	1.09 (0.71-1.68)	1.33 (0.83-2.13)
Tobacco exposure			
Current	53	Ref	Ref
Former	67	1.10 (0.70-1.71)	1.02 (0.60-1.73)
Never	4	1.02 (0.31-3.34)	1.25 (0.36-4.40)
ECOG PS			
0-1	96	Ref	Ref
≥2	28	1.21 (0.73-2.01)	1.35 (0.80-2.28)
Brain metastases			
No	85		
Yes	37	Ref	Ref
Unknown	2	1.30 (0.82-2.08)	1.44 (0.88-2.37)
Liver metastases			
No	105	Ref	Ref
Yes	19	2.09 (1.22-3.58)	1.92 (1.09-3.38)
Age		1.02 (0.99-1.04)	1.020(0.99-1.05)

UVA, univariate analysis; MVA, multivariate analysis; HR, hazard ratio; NOS, not otherwise specified; CI, confidence interval; PD-L1, programmed death-ligand 1; ECOG PS, Eastern Cooperative Oncology Group performance status; Ref, reference.

response to pembrolizumab in other cancers, such as melanoma.[13] Recent studies investigating this potential correlation in NSCLC have reported that patients with NSCLC who have a higher PD-L1 expression, particularly those with expression greater than or equal to 90%, are afforded the most benefit from pembrolizumab therapy, including longer median progression-free survival (PFS) and OS.[11,12,14–16] The magnitude of the difference we saw in the median OS between PD-L1 greater than or equal to 90% and PD-L1 50% to 89% was slightly lower than in other reported studies. One study found that the median OS was not reached for the PD-L1 greater than or equal to 90% group compared with 15.9 months for the PD-L1 50% to 89% group, whereas another study found the median OS to be 30.2 months in PD-L1 greater than or equal to 90% groups compared with 16.9 months in groups with PD-L1 50% to 89%.[12,14] Whereas several studies have identified a treatment advantage in groups with PD-L1 greater than or equal to 90%, a recent study was the first to investigate the long-term benefit of immunotherapy in those with high PD-L1 expression.[17] The study found that the estimates of 3-year PFS were 29.2% and 13.8% for patients with PD-L1 TPS greater than or equal to 90% and 50% to 89%, respectively.[17] Similarly, 3-year OS rates were higher in the PD-L1 greater than or equal to 90% at 46.6% compared with 31.8% in the PD-L1 50% to 89% group, indicating a considerable long-term survival advantage of immunotherapy in those with very high PD-L1 expression.[17] Although many studies have defined very high expression as greater than or equal to 90%, the optimal cut-point is unknown. Our findings support the idea that there is a treatment advantage associated with high PD-L1 expression, but further research is needed to identify where the cutoff for this advantage exists.

Our treatment results varied from those found in the KEYNOTE-024 study.[8] The median number of pembrolizumab cycles completed in our study for those who received pembrolizumab alone was six (range 1-36), compared with the KEYNOTE-024 study, which had a median treatment cycle of 10.5 (range 1-26). Of the patients who received pembrolizumab therapy in the KEYNOTE-024 study, 17 (11.0%) completed a full 2-year treatment cycle, compared with 24 (18.2%) in our study.[18] The median OS was longer in the pembrolizumab group in KEYNOTE-024 than what we observed. However, KEYNOTE-024 only enlisted patients with ECOG PS 0 to 1 and our study had a higher percentage of patients with brain metastases (29.5% compared with 11.7% in KEYNOTE-024). Patients with higher ECOG PS and brain metastases have poorer prognoses, so this may

have contributed to the differences in mean OS between the studies.

All but eight patients in our study received pembrolizumab monotherapy as first-line treatment for their advanced PD-L1–high NSCLC. However, it should be noted that pembrolizumab alone was publicly funded for the duration of the study, whereas the combination therapy was funded at our center starting in mid-2020, likely contributing to the limited number of patients who received combination therapy. As a result, our sample size was too small to compare factors that influence the choice between monotherapy and combination therapy in patients with PD-L1–high NSCLC. However, all patients who received combination therapy had an ECOG PS between 0 and 1, which may have led the prescribing physician to believe that they were better suited for the possible increased toxicity of adding chemotherapy to the treatment regimen. Furthermore, most patients who received combination treatment were women. Multiple studies have indicated improved responses to immunotherapy, and specifically immune checkpoint inhibitor therapy, in men compared with women.[19–21] Of particular note, one study found that male patients with NSCLC exhibited a statistically significant improvement in PFS with anti–PD-1 inhibitors compared with chemotherapy, but female patients did not exhibit the same benefit.[20] Thus, the female sex may be a factor influencing the prescribing of combination therapy over monotherapy in PD-L1–high patients.

Other studies have identified, age, history, and molecular mutation status as factors influencing immunotherapy prescribing patterns. Several studies have found that patients with no tobacco exposure tend to derive less benefit from pembrolizumab monotherapy compared with those who have current or former tobacco exposure.[22–24] In this subgroup, the preferred treatment option is combination therapy. Age is often taken into consideration when making treatment decisions, as older patients often present with more complicated comorbidities and may be less suited for the potentially harmful adverse effects of chemotherapy. One study reported that, in patients with NSCLC treated with immunotherapy, PFS improved with advancing age until age surpassed 80 years, which was the lowest among all age groups. On the other hand, several studies have found immunotherapy to be equally effective in younger and older patients.[25,26] Given the efficacy of immunotherapy in older populations, and the desire to avoid adverse effects associated with chemotherapy, pembrolizumab monotherapy is often the preferred treatment option with increasing age.

Specific genetic mutations can also predict immunotherapy outcomes and, therefore, influence prescribing patterns. Some studies have indicated that patients with KRAS mutations have improved immunotherapy outcomes compared with those who are KRAS wildtype[27,28] Meanwhile, STK11 mutations are associated with immunotherapy resistance and worse overall outcomes in NSCLC.[29–31] Similar findings are present for KEAP1 mutations, in which KEAP1 has been indicated as a predictive biomarker for immunotherapy outcomes, and patients with this mutation exhibited poorer response to immunotherapy.[32,33] Thus, the presence of certain mutations may favor one treatment modality over the other.

Given the small number of patients treated with combination therapy in our study, we were not able to make meaningful survival comparisons between patients treated with combination therapy and those treated with pembrolizumab monotherapy. Several studies have found no difference in OS between the different treatment modalities, despite improvements in PFS and objective response rate (ORR), an early survival advantage in the combination therapy group, and improved outcomes in patients with no tobacco exposure.[34–38] However, a recent pooled analysis of 12 randomized trials evaluating PD-L1 immunotherapy with or without chemotherapy in patients with PD-L1–high NSCLC found that the median OS in the pooled combination therapy group was higher than the immunotherapy monotherapy group (25.0 mo versus 20.9 mo), indicating that chemotherapy and immunotherapy combined may be superior to immunotherapy alone.[39] Whereas some studies have highlighted advantages in the median OS, ORR, and PFS in patients treated with combination therapy compared with pembrolizumab alone, the addition of chemotherapy is often associated with increased toxicity.[40] The current body of research suggests that there are no appreciable differences in OS between the two treatment modalities; however, a prospective randomized trial would be required to elucidate the exact differences in outcomes between the regimens.

In our evaluation of prognostic factors, the multivariate analysis revealed that patients in the PD-L1 50% to 89% group and patients with liver metastasis had poorer OS. Previous studies have indicated that liver metastases could be a prognostic factor for patients with NSCLC receiving immunotherapy.[41] Thus, the presence of liver metastases may not only be a prognostic factor for patients with NSCLC on immunotherapy but it should also be investigated for its importance in choosing between monotherapy and combination therapy regimens.

Our study is limited by its small sample size and its nature as a single-center retrospective study. Because of the small sample size, particularly of the combination therapy group, we were unable to evaluate factors that led to the decision to prescribe combination therapy over pembrolizumab monotherapy. Another limitation

was that we were unable to obtain the exact PD-L1 TPS for eight patients included in our study. These patients were classified as having a PD-L1 expression of greater than or equal to 50% not otherwise specified. Our inability to determine whether these patients fell in the 50% to 89% or greater than or equal to 90% group may have impacted the survival statistics according to PD-L1 expression level. Finally, our study was limited by the use of electronic medical records and physician notes, which varied in quality and completeness. Future research should involve multicenter studies with larger patient populations to better elucidate the factors that may lead to the prescribing of one treatment option over another.

In conclusion, our study provided a comprehensive review of the treatment regimens of all patients at our center who received pembrolizumab for PD-L1–high NSCLC. We found that most patients in this group received pembrolizumab alone, as opposed to combination treatment with chemotherapy. Most notably, we found that for those with very high PD-L1 expression ($\geq$90%) treated with pembrolizumab monotherapy, there is a survival advantage, compared with those with PD-L1 50% to 89%. Our study supports ongoing findings that PD-L1 TPS, rather than the broad cutoff of PD-L1 greater than or equal to 50%, is an important predictive factor for pembrolizumab treatment outcomes. Future studies should investigate which factors would best advise the choice between pembrolizumab monotherapy and combination therapy and should further elucidate the importance of PD-L1 TPS expression in this decision.

CRediT Authorship Contribution Statement

Ashley Jackson: Investigation, Writing – Original draft, Writing – review & editing.

Nina Chang: Investigation, Resources, Writing – review & editing.

Deborah Akurang: Investigation.

Paul Wheatley-Price: Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration.

Sara Moore: Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision, Project administration.

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