Immunotherapy Outcomes in Individuals With Non–Small Cell Lung Cancer and Poor Performance Status

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Abstract

Background: Patients with non–small cell lung cancer (NSCLC) treated in real-world practice typically have worse performance status (PS) compared with clinical trial patients, and the effectiveness of immunotherapy in this population in unknown. In this study, we assessed the effectiveness of standard of care immunotherapy for the first-line treatment of stage IV patients with NSCLC with Eastern Cooperative Oncology Group (ECOG) PS greater than or equal to 2. **Methods:** We selected ECOG PS greater than or equal to 2 patients from real-world oncology data from a deidentified database and included them if they were diagnosed with stage IV NSCLC and had documented Programmed death-ligand 1 [PD-(L)1] expression greater than 0. Patients with tumor PD-(L)1 expression of at least 50% treated with pembrolizumab monotherapy were compared with those who did not have any documented treatment. Patients with tumor PD-(L)1 expression less than 50% treated with pembrolizumab and chemotherapy were compared with those treated with pembrolizumab monotherapy and those without documented treatment. **Results:** In our propensity score–adjusted analysis, patients with ECOG PS of at least 2 and tumor PD-(L)1 expression of at least 50% treated with pembrolizumab monotherapy had statistically significantly better real-world overall survival compared with those without documented treatment (adjusted hazard ratio [HR] = 0.39, 95% confidence internal [CI] = 0.32 to 0.47). For patients with tumor PD-(L)1 expression less than 50%, there was also a statistically significant real-world overall survival benefit for those who received treatment either with combination pembrolizumab plus chemotherapy (adjusted HR = 0.39, 95% CI = 0.32 to 0.46) or pembrolizumab monotherapy (adjusted HR = 0.55, 95% CI = 0.41 to 0.70) compared with patients receiving no documented treatment. **Conclusions:** Among a highly representative sample of patients with advanced NSCLC and poor PS, our findings suggest that immunotherapy may provide an important survival benefit in individuals with high PD-(L)1–expressing tumors and in conjunction with chemotherapy in tumors with low PD-(L)1 expression.

Immune checkpoint inhibitors (ICIs) blocking Programmed death-ligand 1 [PD-1 or PD-(L)1] have changed the treatment landscape of non–small cell lung cancer (NSCLC). ICIs have demonstrated improved efficacy and tolerability compared with standard chemotherapy in several large clinical trials, and these novel drugs are now Food and Drug Administration approved in multiple treatment settings (1-3). However, patients with NSCLC treated in real-world practice typically have worse performance status (PS), with multiple age- and smoking-related comorbidities compared with clinical trial patients (4). Therefore, it is unknown if existing clinical trial data can be extrapolated for patients with Eastern Cooperative Oncology Group (ECOG) PS 2 or higher, leading to a critical gap in knowledge to guide management in clinical practice.

Up to 30%-40% of patients with NSCLC treated in real-world clinical practice have an ECOG PS of 2 or 3 (5). To date, there is no consensus or guidelines for standard treatment of these patients. NSCLC patients with poor ECOG PS are more likely to be affected by treatment-related toxicities, resulting in increased morbidity, mortality, and quality of life detriment. Additionally, patients with poor ECOG PS may have limited benefit from certain treatments due to competing risks of death

from other comorbidities. In fact, NSCLC patients with PS 2 experience lower response rates, shorter time to treatment failure, and worse survival with platinum-based doublet chemotherapy compared with patients with PS 0 or 1 (6). However, it is clear that PS 2 patients still derive survival and quality of life benefit from treatment compared with no treatment, suggesting that the risk-benefit ratio must be recalibrated specific to this population (7).

Newer immunotherapy agents with favorable side effect profiles may offer safe and effective treatment options for NSCLC patients with ECOG PS 2 or 3. Currently, an anti-PD-1 inhibitor (ie, pembrolizumab) is approved for first-line treatment of stage IV patients with NSCLC as monotherapy for PD-(L)1–expressing tumors (≥1%; although normally used alone for PD-(L)1 ≥ 50%) and in combination with chemotherapy regardless of PD-(L)1 expression. Thus far, there has been only 1 prospective phase II study describing the outcomes of first-line pembrolizumab in PS 2 patients (8). However, without a comparator arm and given the small sample size, it remains difficult to make conclusions for treatment decisions in clinical practice. Therefore, the comparative effectiveness of ICIs as monotherapy or in combination with chemotherapy for patients with poor PS still needs to be established.

In this retrospective analysis, we assessed the effectiveness of standard of care immunotherapy (alone or in combination with chemotherapy based on tumor PD-(L)1 expression) for the first-line treatment of stage IV NSCLC patients with ECOG PS greater than or equal to 2 using real-world oncology data from a deidentified database. Specifically, we compared 1) first-line pembrolizumab monotherapy vs no treatment in high PD-(L)1–expressing tumors; and 2) pembrolizumab vs no treatment, pembrolizumab immunotherapy plus platinum-based chemotherapy vs no treatment, and pembrolizumab plus platinum-based chemotherapy vs pembrolizumab alone in low PD-(L)1–expressing tumors.

Methods

Study Cohort

The study cohort was selected using the nationwide Flatiron Health electronic health record-derived deidentified database, which at the time of this study included data from approximately 280 US oncology clinics and approximately 800 sites of care. The Flatiron Health database is a longitudinal database, comprising deidentified patient-level structured and unstructured data curated via technology-enabled abstraction (9). Patients were included if they were diagnosed with stage IV NSCLC, had at least 2 documented clinical visits on or after January 1, 2011, and had documented PD-(L)1 expression greater than 0, ECOG PS of at least 2, and clinical and treatment information recorded within 90 days of diagnosis: in the (≥50%) PD-(L)1 group, documentation of receipt of first-line pembrolizumab or no treatment, in the low PD-(L)1 group, documentation of receipt of first-line pembrolizumab, first-line pembrolizumab plus platinum-based chemotherapy, or no treatment. Stage was confirmed by record abstractors via patient records through pathologic or clinical reports. Flatiron abstractors follow a hierarchy that prioritizes 1) pathologic group stage as documented in the record, unless the patient received neoadjuvant therapy, in which case clinical stage is given preference; 2) clinical stage as documented in the record; 3) in the absence of explicit stage in the record, calculated stage based on the T, N, and M stages

using the most relevant version of American Joint Committee on Cancer based on the patient's diagnosis date. If it is documented that distant metastasis is present at the time of diagnosis, the overall stage is documented as stage IV; and 4) if no group stage or TNM stage is documented and there is no documented distant metastasis, abstractors leave stage at diagnosis incomplete (9).

Patients were stratified by high (≥50%) PD-(L)1 expression and low PD-(L)1 expression. For each patient, baseline characteristics at disease diagnosis were collected, including 1) baseline demographic characteristics (age, sex, race, and ethnicity), smoking status, and ECOG PS (90 days prior to diagnosis to 90 days after diagnosis); 2) tumor characteristics, including histology, mutation status (*EGFR*, *ALK*, *ROS1*, *BRAF*), and PD-(L)1 expression (0%-100% staining); and 3) clinic US census region (Midwest, Northeast, South, West) and Medicaid insurance type.

In patients with high (≥50%) PD-(L)1 expression, in which we compared first-line pembrolizumab vs no documented treatment, our outcome was real-world overall survival (rwOS), defined as time from diagnosis to death (censored at last electronic health record activity) (10). In patients with low PD-(L)1 status, we compared combination pembrolizumab and chemotherapy vs no treatment, combination pembrolizumab and chemotherapy vs pembrolizumab alone, and pembrolizumab vs no treatment. We examined rwOS, median rwOS, as well as real-world progression-free survival (PFS) in these individuals. The real-world PFS was defined as time from diagnosis to clinician documentation of disease worsening (censored at last clinic note date) (11,12). Institutional review board approval of the study protocol for data collection was obtained prior to study conduct and included a waiver of informed consent. This study was determined to be exempt human research by the Institutional Review Board of Mount Sinai Medical Center.

Statistical Analysis

Median rwOS was estimated using weighted Kaplan-Meier methods. We used the marginal structural Cox regression model to estimate the treatment effect on the rwOS and PFS of the patients with NSCLC with poor ECOG PS (13,14). The marginal structural model relates the potential hazard function with the treatment group. Because the treatments were not randomly allocated, the confounding covariates between the treatment groups may not be balanced. We used the inverse probability of treatment weighting separately in each cohort to improve the covariate balance and thereby mitigated the selection bias due to measured confounding. The inverse probability weights were calculated for each individual from a propensity score model in which the outcome was the treatment group indicator and the covariates were the confounding factors (see Table 1). The propensity score model outputs the individual probability of receiving the assigned treatment, the inverse of which is the individual weight. To estimate the weights accurately, we used a flexible ensemble machine-learning technique, Super Learner, for the propensity score model (15). Models in the Super Learner ensemble library included XGBoost, GAM, and Random Forests. When comparing no treatment vs pembrolizumab alone, a binary treatment assignment was used for the Super Learner model; and when comparing 3 treatment groups (no treatment vs pembrolizumab plus platinum-based chemotherapy vs pembrolizumab alone), a nominal treatment assignment was considered (16). To further mitigate the possible issue of extreme weights, we stabilized

Table 1. Characteristics of patients with ECOG PS of at least 2 with NSCLC according to PD-(L)1 status and treatment

Characteristic	PD-(L)1 ≥ 50%			PD-(L)1 < 50%			
	Pembrolizu-mab (n = 546)	No treatment (n = 217)	P[a]	Pembrolizu-mab (n = 87)	Pembrolizu-mab + che-motherapy (n = 280)	No treatment (n = 265)	P[a]
Age, y							
Mean (SD)	72.2 (9.6)	71.7 (9.7)	.53	75.6 (7.7)	68.6 (9.7)	73.0 (8.9)	<.001
Sex, No. (%)							
Female	275 (50.4)	98 (45.2)	.22	40 (46.0)	115 (41.1)	129 (48.7)	.21
Male	271 (49.6)	119 (54.8)		47 (54.0)	165 (58.9)	136 (51.3)	
Race, No. (%)			.41				.90
Asian	9 (1.6)	8 (3.7)		2 (2.3)	5 (1.8)	2 (0.8)	
Black	45 (8.2)	18 (8.3)		10 (11.5)	26 (9.3)	22 (8.3)	
Other race[a]	54 (9.9)	26 (12.0)		9 (10.3)	24 (8.6)	28 (10.6)	
Unknown race	54 (9.9)	19 (8.8)		7 (8.0)	27 (9.6)	28 (10.6)	
White	384 (70.3)	146 (67.3)		59 (67.8)	198 (70.7)	185 (69.8)	
ECOG PS, No. (%)			.001				<.001
2	426 (78.0)	142 (65.4)		69 (79.3)	248 (88.6)	187 (70.6)	
3 and 4	120 (22.0)	75 (34.6)		18 (20.6)	32 (11.4)	78 (29.4)	
Former/current smoking history, No. (%)			.68				.49
Yes	513 (94.0)	201 (92.6)		83 (95.4)	263 (93.9)	244 (92.1)	
No	33 (6.0)	16 (7.4)		4 (4.6)	17 (6.1)	21 (7.9)	
Histology, No. (%)			.06				.001
Non-Sq cell	401 (73.4)	157 (72.4)		50 (57.5)	209 (74.6)	165 (62.3)	
Sq cell	126 (23.1)	44 (20.3)		35 (40.2)	58 (20.7)	89 (33.6)	
NOS	19 (3.5)	16 (7.4)		2 (2.3)	13 (4.6)	11 (4.2)	
Insured by Medicaid, No. (%)	37 (6.8)	27 (12.4)	.02	6 (6.9)	39 (13.9)	25 (9.4)	.56
Community practice, No. (%)	524 (96.0)	210 (96.8)	.75	84 (96.6)	271 (96.8)	255 (96.2)	.94
Practice location, No. (%)			.77				.20
Northeast	113 (20.7)	46 (21.2)		20 (23.0)	72 (25.7)	49 (18.5)	
Midwest	75 (13.7)	29 (13.4)		13 (14.9)	43 (15.4)	36 (13.6)	
South	268 (49.1)	106 (48.8)		35 (40.2)	130 (46.4)	141 (53.2)	
West	59 (10.8)	28 (12.9)		15 (17.2)	24 (8.6)	28 (10.6)	
Other	31 (5.7)	8 (3.7)		4 (4.6)	11 (3.9)	11 (4.2)	

[a]Continuous variables (age) were compared between 2 groups [PD-(L)1 ≥ 50%] using 2-sample t test and among 3 groups [PD-(L)1 < 50%] using 1-way analysis of variance test. Categorical variables were compared using Fisher exact test. All tests were 2-sided test. "Other" race includes American Indian or Alaska Native, Hawaiian or Pacific Islander, and others. ECOG PS = Eastern Cooperative Oncology Group Performance Status; Non-Sq = nonsquamous; NOS = not otherwise specified; NSCLC = non-small cell lung cancer; PD-(L)1 = Programmed death-ligand 1; Sq = squamous.

the estimated weights as suggested by Hernán et al. (14). To assess whether the inverse probability of treatment weighting improved covariate balance, Supplementary Table 1 (available online) compares the weighted standardized difference between the treatment groups (17). Although there is no consensus on a standard threshold to consider as an acceptable measurement of covariate balance, a standardized difference of less than 0.1 to indicate negligible differences between groups has been suggested (17). Finally, a weighted Cox proportional hazards model was fit to estimate the survival treatment effects. The proportional hazards assumption was checked using statistical tests based on the scaled Schoenfeld residuals. Confidence intervals (CIs) of the adjusted hazard ratios (HR) for comparing the treatment groups were computed based on the robust sandwich-type variance estimator for the variance of the estimated hazard ratios (18).

All statistical tests were 2-sided. P less than .05 was considered statistically significant. Continuous variables were compared between 2 groups [PD-(L)1 ≥ 50%] using 2-sample t test and among 3 groups [PD-(L)1 < 50%] using 1-way analysis of variance. Categorical variables were compared among different treatment groups using Fisher exact test.

Results

Of 64 648 patients with advanced NSCLC in the Flatiron database, 1395 ECOG PS ≥2 patients were included based on eligibility criteria (Figure 1). Table 1 describes the differences in baseline characteristics between patients according to treatment groups, stratified by those with high vs low PD-(L)1 expression. Of patients with tumors expressing at least 50% PD-(L)1 (n = 763), 72% received pembrolizumab monotherapy, and 28% received no documented treatment. Patients treated with pembrolizumab monotherapy were statistically significantly more likely to have a better PS (ECOG PS 2 vs PS 3 or 4; P = .001) and less likely to have Medicaid insurance (P = .02) compared with those who did not receive any documented treatment. There were no statistically significant differences in sex, race, smoking history, histology, practice type, or practice location between the pembrolizumab and no-treatment groups (P > .05). For those with PD-(L)1 of at least 50%, the median survival time was 7.1 months and 2.7 months for the patients treated with pembrolizumab vs no documented treatment group, respectively. In our propensity score–adjusted analysis, patients with ECOG PS of at least 2 and tumor PD-(L)1
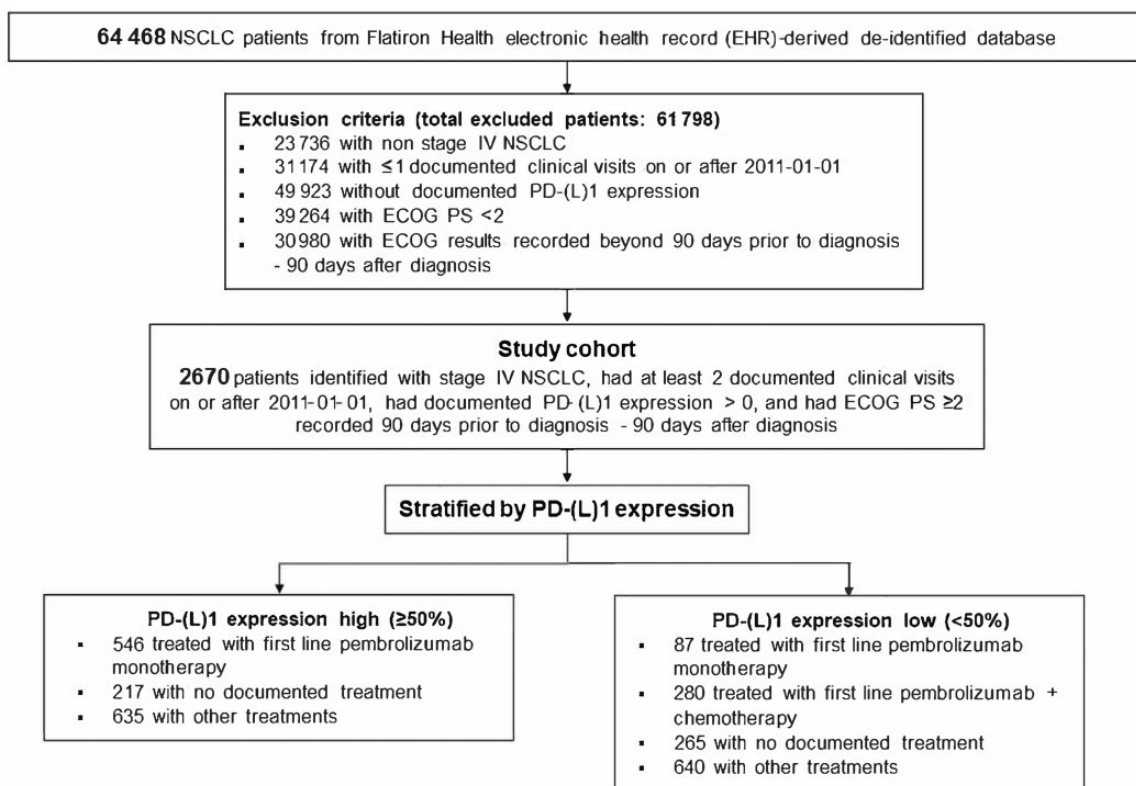
Figure 1. CONSORT diagram. ECOG PS = Eastern Cooperative Oncology Group Performance Status; NSCLS = non–small cell lung cancer; PD-(L)1 = Programmed death-ligand 1.

expression of at least 50% treated with pembrolizumab monotherapy had statistically significantly better rwOS compared with those who did not receive any documented treatment (adjusted HR = 0.39, 95% CI = 0.32 to 0.47; Figure 2).

Of patients with NSCLC with tumors expressing less than 50% PD-(L)1 (N = 632), 44.3% (n = 280) received pembrolizumab plus platinum-based chemotherapy, 13.7% (n = 87) received pembrolizumab monotherapy, and 41.9% (n = 265) received no documented treatment (Table 1). When comparing these groups, patients receiving pembrolizumab plus platinum-based chemotherapy were more likely to be younger (P < .001) and have nonsquamous histology (P = .003) compared with patients receiving pembrolizumab monotherapy. Patients who received no documented treatment were more likely to have ECOG PS 3 or 4 (P < .001) compared with those received pembrolizumab + chemotherapy. All other baseline covariates were well balanced between treatment groups (P > .05).

For patients with tumor PD-(L)1 expression less than 50%, there was also a statistically significant rwOS benefit for those who received treatment, either with combination pembrolizumab plus chemotherapy (adjusted HR = 0.39, 95% CI = 0.32 to 0.46) or pembrolizumab monotherapy (adjusted HR = 0.55, 95% CI = 0.41 to 0.70) compared with patients receiving no documented treatment (Figure 2).

When comparing low–PD-(L)1 patients receiving pembrolizumab monotherapy vs pembrolizumab plus chemotherapy, no statistically significant difference in rwOS (adjusted HR = 0.80, 95% CI = 0.53 to 1.10) or rwPFS (adjusted HR = 0.99, 95% CI = 0.64 to 1.37) was observed (Figure 2). The median survival time in months as 2.6, 5.6, and 7.9 for the not documented treatment group, pembrolizumab group, and

pembrolizumab + chemotherapy group, respectively. The median PFS time is 7.7 months and 7.9 months for the pembrolizumab group and pembrolizumab + chemotherapy group, respectively.

Discussion

Because ECOG PS is a major indicator of tolerability and response to cancer treatment, it is unknown if the survival benefit demonstrated in ICI trials is observed in patients with NSCLC with PS 2 or higher treated in clinical practice. Using real-world data from the Flatiron Health database, we found in our adjusted survival analysis that patients with ECOG PS of at least 2 indeed had a statistically significant OS benefit with ICI treatment, either alone or in combination with chemotherapy depending on PD-(L)1 expression, compared with not receiving treatment. In the low–PD-(L)1 expression (<50%) cohort, where ICI is routinely used in combination with chemotherapy, we found that ICI monotherapy provided similar OS for patients with ECOG PS of at least 2. Therefore, our findings suggest first-line ICI treatment should be routinely used in all NSCLC patients who are eligible, regardless of ECOG PS.

ECOG PS is a clinical scale that describes increasing levels of disability from cancer-related symptoms and/or underlying comorbidities and has traditionally been used to assess risks and benefits for treatment decisions related to chemotherapy. When compared with PS 0 or 1 patients, patients with PS of at least 2 have consistently been shown to derive less survival benefit with increased exposure to toxicity with platinum-based doublet chemotherapy (6). In the pooled analysis of 5 ECOG chemotherapy randomized controlled trials, PS 2 patients
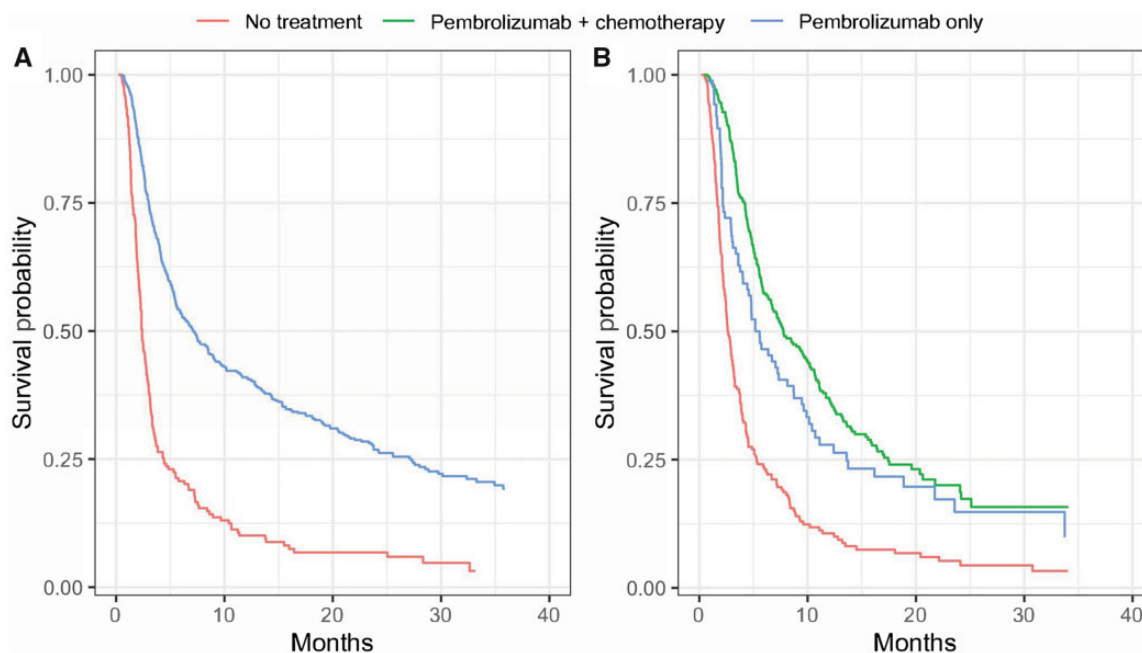
Figure 2. Adjusted overall survival curves based on Cox models comparing treatment with pembrolizumab monotherapy, pembrolizumab plus chemotherapy and no treatment in patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) of at least 2 with non–small cell lung cancer (NSCLC) according to Programmed death-ligand 1 [PD-(L)1] expression (A) greater or equal to 50% and less than 50% PD-(L)1 expression (B).

had statistically significantly lower OS compared with PS 0 or 1 patients, with 1-year survival rates less than 20% ([19]). Furthermore, the large phase III ECOG Study E1594 comparing 4 platinum-based chemotherapy combinations stopped enrolling PS 2 patients after higher excess adverse events and 7.6% grade 5 toxicities among this group ([6]). These and other studies raise concerns that patients with PS2 require special treatment consideration and guidelines remain controversial.

ICIs in NSCLC may shift the risk-benefit ratio in favor of treatment for PS 2 patients. However, ICI randomized controlled trials have largely excluded PS 2 patients, once again leaving clinicians to suboptimally extrapolate data to this group. Thus far, the Pembrolizumab in Patients with Non-Small Cell Lung Cancer of Performance Status 2 trial is the only phase II, single-arm trial that prospectively evaluated outcomes of ICI monotherapy in PS 2 patients ([8]). Although the study rigorously screened for PS 2 patients, important limitations including small sample size, clinical heterogeneity in the study cohort [eg, first- vs second-line treatment, PD-(L)1 low vs high expression] and lack of a comparator arm made meaningful conclusions challenging. Recent observational studies have attempted to compare ICI outcomes in PS 2 patients vs PS 0 or 1 patients ([20-22]). However, these studies are single institution, also have small sample sizes, and do not evaluate the efficacy of different treatment approaches in patients with PS of at least 2. To our knowledge, this study is the first to evaluate ICI treatment, as monotherapy or in combination with chemotherapy, compared with no treatment using a large and highly representative database. Our novel findings that ICI treatment provides statistically significant benefit in NSCLC patients with PS greater than or equal to 2 should help guide the management of these patients.

For patients with PD-(L)1 low– (1%-49%) expressing NSCLCs, treatment with ICI is approved as both monotherapy and in combination with chemotherapy following the results of

Keynote 024 and Keynote 189/407 trials, respectively, showing improved survival outcomes compared with first-line chemotherapy ([1]). For this indication, combination ICI plus chemotherapy more clearly demonstrated benefit and is therefore considered standard of care. Although the addition of ICI did not seem to synergistically worsen toxicities, patients still experienced both chemotherapy and immune-related toxicities. There has not been a prospective trial reported directly comparing ICI monotherapy vs combination with chemotherapy, especially in poor PS patients where the omission of chemotherapy would likely be more tolerable. To our knowledge, our study is the first to show that the OS and PFS of ICI monotherapy is similar to combined ICI and chemotherapy in PD-(L)1–low patients with poor PS.

There are several strengths to our real-world study examining the impact of immunotherapy in individuals with NSCLC with poor PS. Notably, patients with poor PS are a cohort traditionally excluded from clinical trials, and PS is not routinely captured in other large cancer registries or claims-based datasets. This study, using the Flatiron real-world database, provides PS, PD-(L)1 status, treatment information, as well as clinical response from both structured and unstructured clinical documents from community-based oncology practices, allowing long-term follow-up as well as determination of PFS. In addition to the strengths, there are also several limitations that must be taken into consideration. Because study patients are not randomly assigned to treatments but rather are selected based on several clinical factors, systematic differences in the distribution of pretreatment characteristics between treatment groups could potentially influence clinical outcomes. To mitigate this selection bias, we applied propensity score methods to balance groups for all other measured confounders, such as presence and severity of comorbidities. However, we were unable to account for unmeasured confounders, such as presence

and severity of comorbidities, which may drive treatment decisions because they were not available in the structured data or routinely collected. However, we expect that most treatment-driving comorbidities are likely captured and represented in the PS as well. Additionally, there is the potential limitation of immortal time bias due to comparing a treated group with a group without documented treatment. It is possible that patients in the group without documented treatment would have gone on to receive treatment but died before they could begin treatment. However, the weighted model adjusts for nonrandom treatment allocation using baseline confounders. If a patient's death occurred prior to receipt of treatment, it should be reflected in the baseline covariates, which are in turn adjusted by the weight estimator. Similarly, missing-ness in PS limited our cohort size, and there is potential misclassification among patients without documented treatment if they received treatment outside the Flatiron Health network.

Despite these limitations, our study adds to the growing body of research regarding the effectiveness of immunotherapy in individuals with poor PS. Our real-world study of NSCLC patients with ECOG PS of at least 2 suggests that immunotherapy may provide an important survival benefit. Furthermore, our findings suggest that ICI alone may be a treatment option in poor PS patients with PD-(L)1 low-expressing tumors. Until future randomized studies comparing immunotherapy with best supportive care in this important and common NSCLC subgroup are reported, our findings add to the literature regarding the optimal management of these patients.

Funding

Notes

Data Availability

The data that support the findings of this study have been originated by Flatiron Health, Inc and are not publicly available, in order to safeguard the terms that ensure that the data remain deidentified. These deidentified data may be made available upon request and are subject to a license agreement with Flatiron Health; interested researchers should contact dataaccess@flatiron.com to determine licensing terms.

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