ORIGINAL ARTICLE

Real-World Treatment Patterns and Outcomes Among Patients With Metastatic NSCLC Previously Treated With Programmed Cell Death Protein-1/ Programmed Death-Ligand 1 Inhibitors

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ABSTRACT

Introduction: Programmed cell death protein-1 (PD-1)/ programmed death-ligand 1 (PD-L1) inhibitors are standard-of-care treatment for metastatic NSCLC (mNSCLC). Intolerance to treatment/disease progression warrants additional lines of therapy. Real-world treatment patterns and efficacy outcomes after PD-1/PD-L1 use are insufficiently characterized to inform treatment decisions.

Methods: Electronic health records of adults with stage IV NSCLC initiating PD-1/PD-L1 inhibitors as first-line monotherapy (cohort 1), first-line combination therapy (cohort 2), or second-line monotherapy (cohort 3) who received a subsequent line of therapy (i.e., index therapy) in the Flatiron NSCLC Core Registry Dataset were identified. Patient characteristics, types of index treatments/therapies, and associated index treatment outcomes were extracted.

Results: A total of 1061 patients with mNSCLC were included in this analysis. In cohort 1 (n = 242), median real-world overall survival (mrwOS) with index therapies for the overall population was 9.18 months (95% confidence interval: 7.54–12.13); platinum-based chemotherapy was the most common index therapy (39.3%) with mrwOS of 12.52 months (8.39–not applicable). In cohort 2 (n = 145), mrwOS for the overall population was 6.43 months (5.34–7.61); vascular endothelial growth factor inhibitor plus chemotherapy was the most common index therapy (32.4%) with mrwOS of 5.97 months (4.95–7.34). In cohort 3 (n = 647), mrwOS for the overall population was 7.21 months (6.39–7.80); single-agent chemotherapy was the most common index therapy (45.4%) with mrwOS of 6.59 months (5.64–7.61).

Conclusions: Real-world treatment patterns and survival outcomes of index therapies in mNSCLC after PD-1/PD-L1 use are variable. These analyses provide insights to optimize post–PD-1/PD-L1 treatments and inform standards of care.

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Keywords: Immunotherapy; Non–small cell lung cancer; Programmed death-ligand 1; Real world; Treatment patterns

Introduction

Lung cancer is the leading cause of cancer-related death in the United States,[1] with more than half of

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patients presenting with stage IV (metastatic) disease at diagnosis; the 5-year survival rate is 21.7%.[2,3] In the past 5 years, a number of immune checkpoint inhibitors targeting programmed cell death protein-1 (PD-1) or programmed death-ligand 1 (PD-L1) have gained regulatory approval for the treatment of metastatic NSCLC (mNSCLC).[4–6] Although these agents were initially approved and used in second or later lines of treatment,[7] in current clinical practice they are now more commonly used as first-line therapy for metastatic disease, either alone (tumors with >50% of cells positive for PD-L1) or in combination with platinum-based cytotoxic therapy (tumors with ≤50% of cells positive for PD-L1).[5] In each setting, PD-1/PD-L1 inhibitors have improved survival for patients with mNSCLC.[5]

The integration of immune checkpoint inhibitors as a first-line systemic treatment option has created new challenges. Data on treatment patterns after completing PD-1/PD-L1 inhibitor therapy and clinical outcomes associated with these subsequent lines of therapy have been limited to date. Agents previously used after platinum-doublet therapy remain available after PD-1/PD-L1 inhibitor therapy as well. However, the effectiveness of these regimens after discontinuation of PD-1/PD-L1 inhibitor therapy has, to our knowledge, not yet been extensively reported from controlled trials. Such information is important to inform clinical decision-making and to identify treatment gaps and unmet needs in the continuum of care for patients with NSCLC, and this information can be of critical importance for null-hypothesis generation in clinical trial designs.

The data sources used to assess real-world treatment patterns include patient registries, insurance claims databases, and electronic health records (EHRs). One such data source is the Flatiron database (Flatiron, New York, NY), which comprises structured and unstructured data collected from health care providers, including EHRs and billing information. In the Flatiron database, data are standardized to a common model that can be used to investigate real-world patient outcomes. The database includes information from 2.1 million patients from more than 265 community and academic clinics, representing more than 2500 cancer clinicians and approximately 20% of all U.S. patients with active cancer. Thus, this database presented an opportunity to generate a longitudinal view of treatment patterns and outcomes for patients with mNSCLC in the United States.

Accordingly, the present study aimed to describe real-world treatment patterns and survival outcomes for index therapy after PD-1/PD-L1 in the first- or second-line setting in patients with mNSCLC.

Materials and Methods

Study Design

Data from adult patients aged ≥18 years with stage IV NSCLC were extracted from EHRs held in the Flatiron NSCLC Core Registry Dataset (Flatiron) and were retrospectively analyzed. All records included information beginning with a patient's date of diagnosis with mNSCLC until the end of the patient's record, death, or date of data cutoff (April 30, 2019) (Fig. 1). Extracted data included information on demographic and disease characteristics, treatments received, and survival outcomes.

All patients eligible for inclusion in this study had received a new diagnosis of stage IV, stage IVA, or stage IVB NSCLC on or after January 1, 2011 (International Classification of Diseases, Ninth Revision, 162.x or International Classification of Diseases, Tenth Revision, C34x or C39.9); had ≥2 documented clinical visits to a health care provider participating in the Flatiron network on or after January 1, 2011; and were treated with a PD-1/PD-L1 inhibitor (i.e., nivolumab, pembrolizumab, or atezolizumab), either as monotherapy in the first- or second-line setting or as first-line therapy in combination with chemotherapy or a vascular endothelial growth factor inhibitor (VEGFi). Treatment must have been initiated on or after March 4, 2015, the date on which the first PD-1/PD-L1 therapy indicated for the treatment of mNSCLC was approved for use by the US Food and Drug Administration. Patients must also have initiated treatment with the index therapy on or before October 31, 2018, to allow for ≥6 months of follow-up before data cutoff on April 30, 2019. The subsequent line of therapy initiated after PD-1/PD-L1 therapy was defined as the index therapy for all analyses. Chemotherapy was defined as a single-agent or combination chemotherapy regimen, with or without concomitant VEGFi therapy.

Patients eligible for inclusion in this analysis were further classified into three subcohorts defined by treatment regimen: first-line PD-1/PD-L1 monotherapy (cohort 1), first-line PD-1/PD-L1 plus chemotherapy (cohort 2), or first-line chemotherapy followed by second-line PD-1/PD-L1 monotherapy (cohort 3).

Patients with a >90-day gap between the date of mNSCLC diagnosis and the first postdiagnosis structured activity were excluded from the study. Likewise, patients with a documented *EGFR* mutation or *ALK* rearrangement for ≤30 days after the start of the index therapy, with a diagnosis of NSCLC, or with stage I-III NSCLC or unknown staging were not eligible for this study. Antineoplastic agents initiated within 28 days of each other were considered to comprise a single line of therapy.

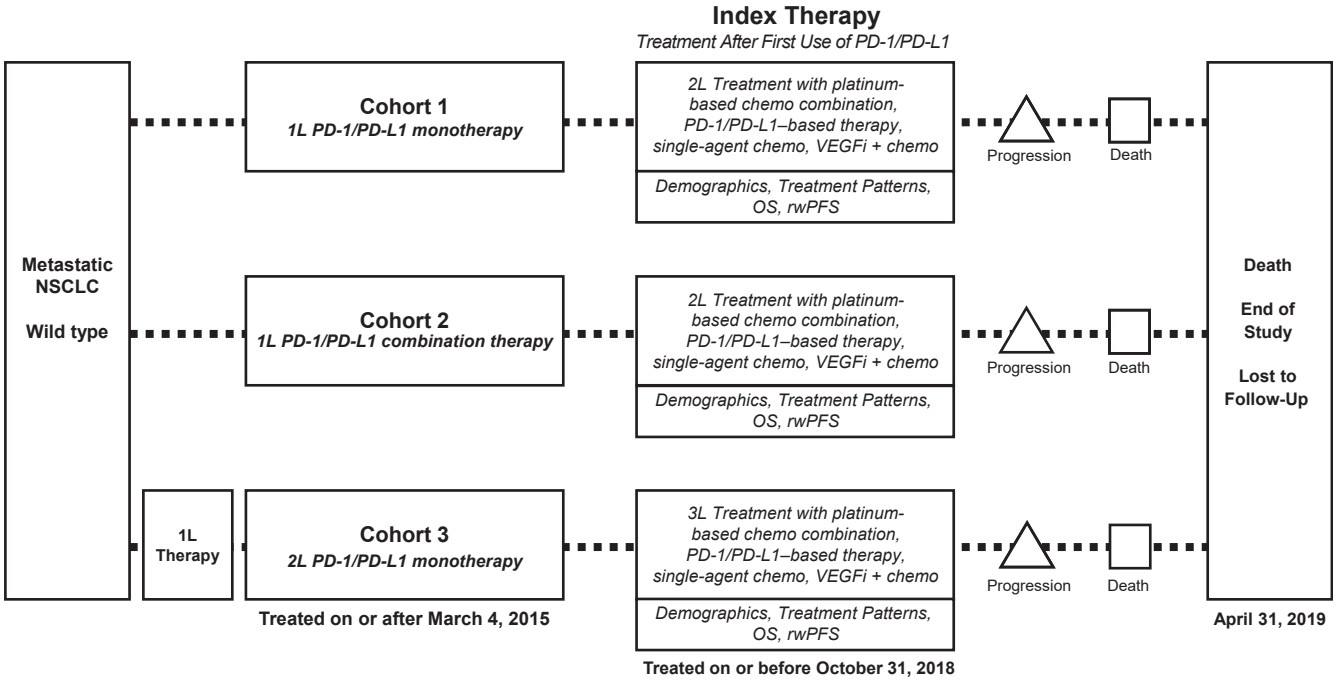

Figure 1. Study design. 1L, first-line; 2L, second-line; 3L, third-line; chemo, chemotherapy; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; rwPFS, real-world progression-free survival; VEGFi, vascular endothelial growth factor inhibitor.

Any switch of therapy or addition of a new agent to an ongoing therapy regimen after $\geq$28 days was considered to represent a new line of therapy. In addition, evidence of disease progression was not a requirement for line of therapy advancement in this analysis.

Study Objectives

The first objective was to describe the demographics, clinical characteristics, and treatment outcomes of the analysis population. The second objective was to describe real-world treatment patterns, including the line of therapy in which a PD-1/PD-L1 inhibitor was initiated and treatments received before (if applicable) and after. The third objective was to describe real-world outcomes, including real-world overall survival (rwOS) and real-world progression-free survival (rwPFS), with the index therapy used after the initial PD-1/PD-L1 inhibitor regimen.

Ethics

All data were collected in the Flatiron NSCLC Core Registry. Flatiron received a waiver of informed consent, and Health Insurance Portability and Accountability Act of 1996 authorization was granted by an independent institutional review board. All data sets were certified as deidentified by the expert determination method prior to patient-level data being released for analysis.

Statistical Analysis

Patient demographic and clinical characteristics were described using means, SDs, medians, and interquartile ranges (as applicable) for continuous variables; frequencies and percentages were used for categorical variables. Real-world treatment patterns among patients receiving PD-1/PD-L1 inhibitors were assessed by reporting the number and proportion of patients receiving each type of index therapy (i.e., treatment class and regimen name), stratified by the PD-1/PD-L1 inhibitor administered directly prior to the index therapy and the setting of the PD-1/PD-L1 inhibitor (i.e., first-line monotherapy, first-line combination therapy, or second-line therapy). Given the descriptive nature of this study, no sample size calculations were performed.

Time-to-event outcomes were estimated using a Kaplan-Meier analysis. Real-world time to treatment discontinuation was defined as the time from index date to discontinuation of the index therapy, with patients censored at the date of last activity. rwPFS was defined as the time from index date to first progression event, with patients censored at the date of last clinic note. rwOS was defined as the time from index date to death, with patients censored at the date of last activity if the date of death was not included in the Flatiron database.

A post hoc analysis was performed to further evaluate the treatment-related details of patients from cohorts 1 and 2 who specifically received PD-1/PD-L1 as

their index therapy. The analysis in this specific population (i.e., "PD-1/PD-L1 retreated") was conducted due to the absence of the requirement of disease progression to define line of therapy advancement per the analysis methodology.

Results

In total, 34,153 patient records from the Flatiron NSCLC Core Registry Dataset were identified as having a de novo diagnosis of mNSCLC on or after January 1, 2011 (Fig. 2). Of these, 1188 patients initiated their first PD-1/PD-L1 treatment between March 4, 2015, and August 31, 2018. After excluding patients with *ALK*, *BRAF*, *EGFR*, or *ROS1* abnormalities, 1061 patients were eligible for inclusion in the study (cohort 1, n = 242; cohort 2, n = 145; cohort 3, n = 674) (Fig. 2).

Key baseline demographics and disease characteristics in the overall study population are summarized in Table 1. Patients had a median age of 67 years at diagnosis and 68 years when index therapy was initiated. Likewise, the prevalence of nonsquamous cell carcinoma was higher in cohort 2 versus cohorts 1 and 3 (89.7% versus 69.4%–70.7%). Patients receiving first-line PD-1/PD-L1 combination therapy (cohort 2) were also younger than those receiving first- (cohort 1) or second-line PD-1/PD-L1 monotherapy (cohort 3) (median age: 64.0 y versus 68.0–72.0 y). Pembrolizumab was the PD-1 inhibitor most often prescribed as first-line therapy (monotherapy, 77.7%; combination therapy, 98.6%), whereas most patients treated with second-line PD-1/PD-L1 monotherapy received nivolumab (84.6%).

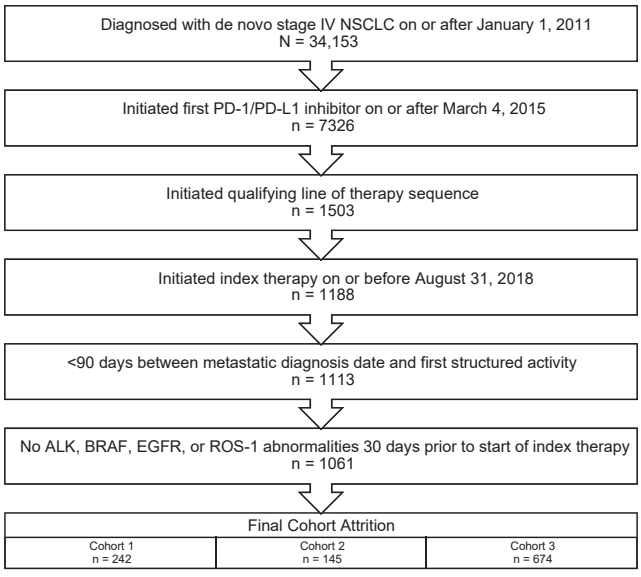

Figure 2. Attrition diagram of study cohort. PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1.

In cohort 1, which comprised patients receiving first-line PD-1/PD-L1 monotherapy, median rwOS with index therapies for the overall cohort was 9.18 months (95% confidence interval [CI]: 7.54–12.13). The most common index therapies used in this group were platinum-based chemotherapy combination therapies (39.3%) followed by PD-L1–based regimens (27.7%) (Fig. 3). It is important to note that disease progression was not a requirement for line of therapy advancement in this analysis and that among patients in cohort 1 with PD-1/PD-L1 index therapy, fewer than 10% initiated index therapy within 60 days of first PD-1/PD-L1 use; this could represent a gap in therapy. Furthermore, 34 (51%) patients continued treatment with their first-line PD-1/PD-L1 inhibitor with the addition of other agents.

Among patients in cohort 1 who received subsequent platinum-based chemotherapy combination therapies, rwOS was 7.44 months and could not be evaluated in patients with a PD-L1–based index therapy. The longest median rwOS observed in cohort 1 (12.52 mo) was associated with the third most common index treatment in this group, VEGFi plus chemotherapy (16.5%) (Fig. 4*A*). This index therapy was also associated with the longest median rwPFS (5.97 mo), whereas the shortest median rwPFS (4.07) was observed with platinum-based chemotherapy combinations (Fig. 5*A*). The predominant combination of VEGFi with chemotherapy used in this cohort and in the overall study was ramucirumab plus docetaxel, although other combinations were possible (i.e., bevacizumab plus carboplatin plus either pemetrexed or paclitaxel).

In cohort 2, which comprised patients who received first-line PD-1/PD-L1 combination therapy, median rwOS with index therapies for the overall cohort was 6.43 months (95% CI: 5.34–7.61). The most common index therapies used in this group were VEGFi plus chemotherapy (32.4%) and single-agent chemotherapy (27.6%) (Fig. 3). Patients treated with a PD-L1–based regimen as index therapy comprised 22.1% of the cohort. rwOS was similar irrespective of index therapy (range: 5.97–7.02 mo) (Fig. 4*B*). Interestingly, median rwPFS, which was similar across index therapies received after first-line PD-1/PD-L1 inhibitor monotherapy, ranged from 2.56 to 3.41 months and was generally lower than that observed for cohort 1 (Fig. 5*B*).

In cohort 3, which comprised patients receiving second-line PD-1/PD-L1 monotherapy, median rwOS with index therapies for the overall cohort was 7.21 (95% CI: 6.39–7.80) months. The most common index therapy used in this group was single-agent chemotherapy (45.5%) (Fig. 3). rwOS in this group (6.59 mo) was similar to that observed in patients who received chemotherapy plus a VEGFi (6.92 mo) or platinum-based chemotherapy (6.23 mo). Prolonged

Table 1. Key Baseline Patient Demographics and Clinical Characteristics Stratified by Treatment-Line Setting of First PD-1/PD-L1 Inhibitor

Variable	All Patients N = 1061	1L PD-1 Monotherapy (Cohort 1) (n = 242)	1L PD-1/PD-L1 Combination Therapy (Cohort 2) (n = 145)	2L PD-1 Monotherapy (Cohort 3) (n = 674)	*p* Value[a]
Age (y) at initial diagnosis of metastatic NSCLC, median [IQR]	67.0 [59.0-74.0]	71.0 [62.0-78.0]	63.0 [57.0-71.0]	67.0 [59.2-74.0]	<0.001
Age (y) at index date,[b] median [IQR]	68.0 [60.0-76.0]	72.0 [63.0-79.0]	64.0 [58.0-72.0]	68.0 [61.0-75.0]	<0.001
History of smoking, n (%)	963 (90.8)	217 (89.7)	133 (91.7)	613 (90.9)	0.766
ECOG PS at index date, n (%)[c]					0.381
0	172 (16.2)	36 (14.9)	33 (22.8)	103 (15.3)	
1	399 (37.6)	90 (37.2)	53 (36.6)	256 (38.0)	
2	191 (18.0)	48 (19.8)	26 (17.9)	117 (17.4)	
3	17 (1.6)	2 (0.8)	3 (2.1)	12 (1.8)	
Unknown, n (%)	282 (26.6)	66 (27.3)	30 (20.7)	186 (27.6)	
Histology at initial diagnosis, n (%)					<0.001
Nonsquamous cell carcinoma	769 (72.5)	171 (70.7)	130 (89.7)	468 (69.4)	
Squamous cell carcinoma	252 (23.8)	61 (25.2)	6 (4.1)	185 (27.4)	
Not otherwise specified	40 (3.8)	10 (4.1)	9 (6.2)	21 (3.1)	
First PD-1/PD-L1 inhibitor received in the first- or second-line metastatic setting, n (%)					<0.001
Atezolizumab	33 (3.1)	2 (0.8)	0 (0.0)	31 (4.6)	
Nivolumab	624 (58.8)	52 (21.5)	2 (1.4)	570 (84.6)	
Pembrolizumab	404 (38.1)	188 (77.7)	143 (98.6)	73 (10.8)	
PD-L1 tested, n (%)					<0.001
Yes	643 (60.6)	211 (87.2)	135 (93.1)	297 (44.1)	
No	418 (39.4)	31 (12.8)	10 (6.9)	377 (55.9)	
PD-L1 percent staining (among those tested), n (%)					<0.001
≥50%	273 (42.5)	172 (81.5)	34 (25.2)	67 (22.6)	
1%-49%	125 (19.4)	9 (4.3)	36 (26.7)	80 (26.9)	
<1%	151 (23.5)	9 (4.3)	54 (40.0)	88 (29.6)	
Unknown	94 (14.6)	21 (10.0)	11 (8.1)	62 (20.9)	
Time on any first-line PD-1/PD-L1 inhibitor (mo), median [IQR]	4.6 [2.8-8.1]	5.0 [2.9-8.8]	4.8 [2.8-7.6]	4.3 [2.8-7.8]	0.164
Follow-up time from index date (mo),[b] median [IQR]	5.3 [2.1-10.1]	6.1 [2.6-11.2]	4.8 [1.8-7.8]	5.0 [2.1-9.9]	0.028
Record of real-world progression event within 6 wk after the last dose of any first-line PD-1/PD-L1 inhibitor, n (%)					
Yes	681 (64.2)	142 (58.7)	87 (60.0)	452 (67.1)	
No	380 (35.8)	100 (41.3)	58 (40.0)	222 (32.9)	Not tested

[a]Comparisons will be made using the chi-square test or the Fisher's exact test (where the expected frequency is <5). A two-sided significance level of $\alpha = 0.05$ was used for all tests and $P < \alpha$ was considered statistically significant.

[b]Index date was defined as the date of initiation of subsequent therapy after the first initiation of PD-1/PD-L1 inhibitor in the metastatic setting.

[c]ECOG PS status closest to the index date (among observations up to 45 d before the index date or up to 14 d after the index date). If there were multiple ECOG PS values with the same absolute distance from the index date, priority was given to the ECOG PS value that preceded the index date. For patients with multiple ECOG PS values recorded on the same day, the highest numerical value was selected. For the purposes of confidentiality, ECOG PS values of 5 were dropped.

1L, first-line; 2L, second-line; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; PS, performance status.

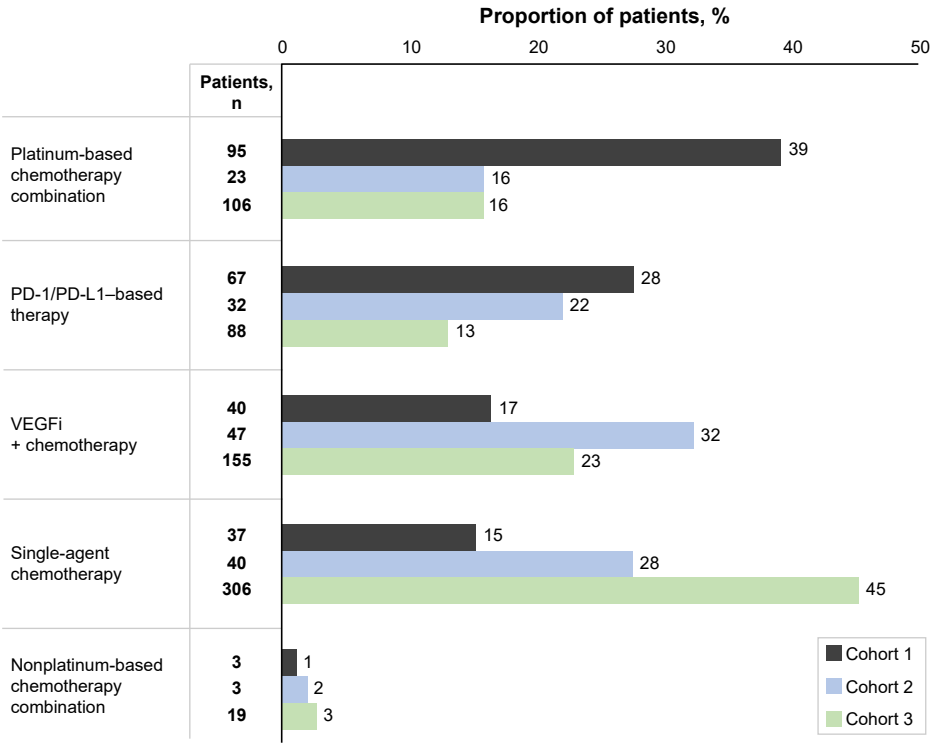

Figure 3. Index therapy: treatment patterns in the study group. PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; VEGFi, vascular endothelial growth factor inhibitor.

rwOS of 11.08 months was observed in patients who received PD-L1–based treatment as index therapy; these patients comprised 13.1% of the cohort (Fig. 4*C*). Median rwPFS was similar across index therapies and ranged from 3.21 to 4.00 months (Fig. 5*C*).

Discussion

The first-line use of PD-1/PD-L1 inhibitors has increased in recent years and has improved outcomes for patients with NSCLC.[7] This has led to a modified treatment model, in which agents previously used as first-line treatment remain available for later lines of therapy. It is therefore important to understand what treatments are being used as subsequent lines of therapy in the real world and their relative effectiveness in patients who are PD-1/PD-L1 experienced.

In this study, 1061 patients with mNSCLC were identified from a longitudinal database. Among those receiving PD-1/PD-L1 inhibitors as first-line treatment, most received pembrolizumab: 78% as a monotherapy in cohort 1 and 99% as combination in cohort 2. Overall, in the first-line setting, PD-1/PD-L1 monotherapy was more often prescribed in patients with high PD-L1 staining in their tumor tissue (≥50% PD-L1 staining) compared with PD-1/PD-L1 combination treatment (81.5% versus 25.2%, respectively); conversely, the PD-1/PD-L1 combination was more commonly prescribed than PD-1/PD-L1 monotherapy in patients with lower percentage of PD-L1 staining (<50%) in their tumor tissue (74.8% versus 18.6%, respectively). These data reflect the timeline of approval of these agents in their respective settings and the adoption of the agents in real-world clinical practice.

The choice of subsequent therapy may seem obvious. Eligible patients who progressed on or after PD-L1 monotherapy would receive platinum-based chemotherapy as the index therapy and those who progressed on or after PD-L1 combination therapy may be treated with chemotherapy alone or in combination with VEGFi. Although platinum-based chemotherapy is recommended as a second-line intervention after PD-1/PD-L1 monotherapy,[6,8] this study reveals considerable heterogeneity in actual treatments administered. In patients receiving treatment after first-line PD-1/PD-L1 inhibitor monotherapy, in addition to platinum-based chemotherapy (39%), 27.7% were treated with PD-1/PD-L1–based therapy, 17% with VEGFi plus chemotherapy, 15.3% with single-agent chemotherapy, and 1.2% with non–platinum-based combination chemotherapy. In patients initially treated with first-line PD-1/PD-L1 combinations, the most common index therapy was single-agent chemotherapy alone or a VEGFi plus chemotherapy, but a small proportion received PD-1/PD-L1–based therapy, platinum-based chemotherapy, or nonplatinum combination chemotherapy. The rwOS reported for index therapy of VEGF inhibitor plus

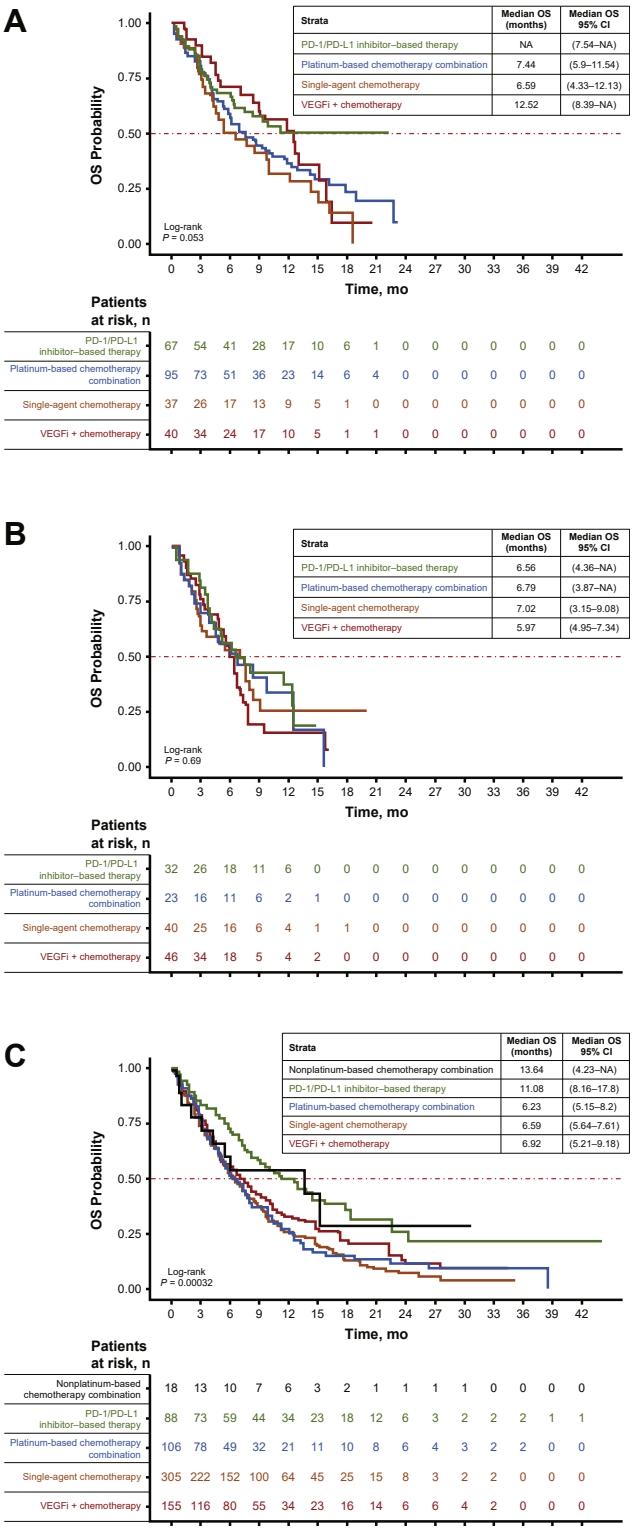

Figure 4. Kaplan-Meier curve of OS from index date stratified by index therapy class after (*A*) first-line PD-1 inhibitor monotherapy, (*B*) first-line PD-L1 inhibitor combination, and (*C*) second-line PD-1 inhibitor monotherapy. CI, confidence interval; NA, not applicable; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; VEGFi, vascular endothelial growth factor inhibitor.

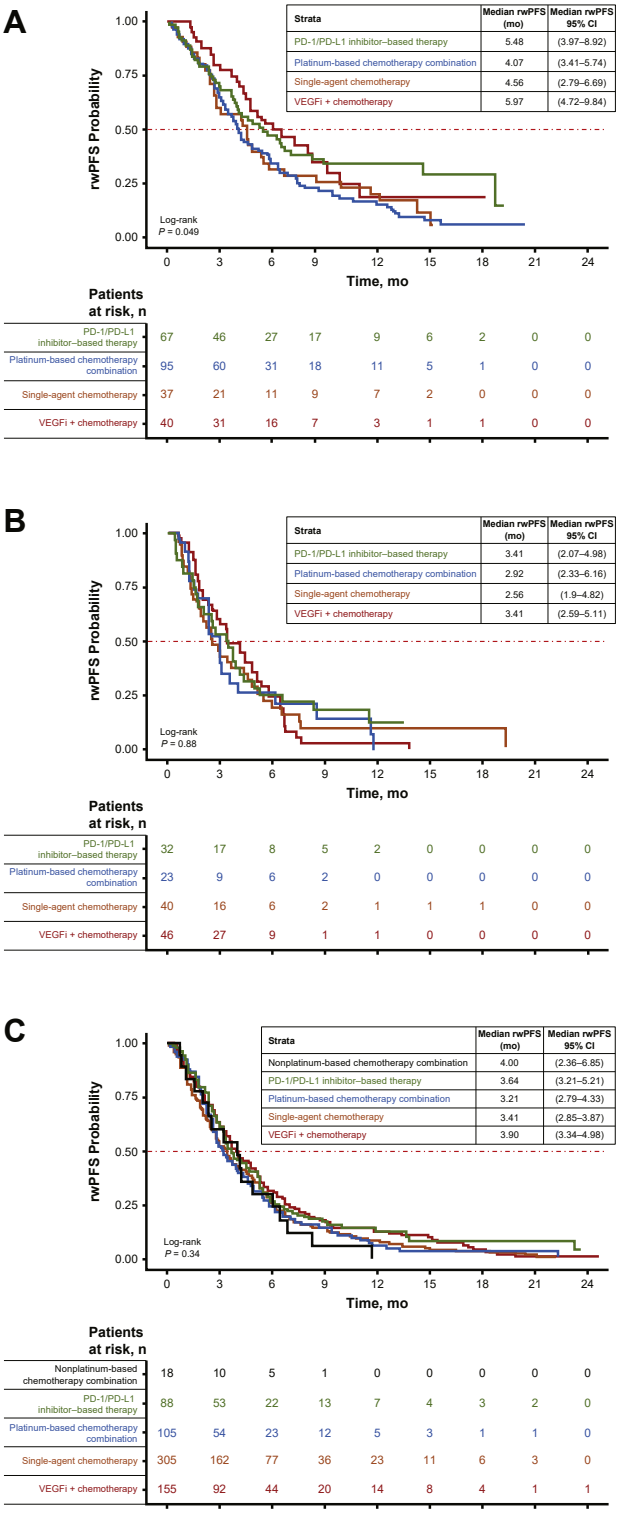

Figure 5. Kaplan-Meier curve of (*A*) rwPFS from index date stratified by index therapy class after first-line PD-1 inhibitor monotherapy, (*B*) first-line PD-1/PD-L1 inhibitor combination, and (*C*) second-line PD-1 inhibitor monotherapy. CI, confidence interval; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; rwPFS, real-world progression-free survival; VEGFi, vascular endothelial growth factor inhibitor.

chemotherapy (5.97 mo, n = 47) does raise questions regarding selection of efficacious treatment regimens in the absence of proper clinical trial data. It is important to note that there are many caveats to the interpretation of these data, especially considering the limitations associated with real-world data, including differences in patient populations and measurements of outcomes compared with controlled clinical trials. Clinical trials in the post–PD-1/PD-L1 setting should be conducted to understand the efficacy of drug regimens.

Overall, rwOS in this study was generally aligned with other published real-world data for patients with NSCLC treated with PD-1/PD-L1 inhibitors.[9,10] Patients treated first-line with PD-1/PD-L1 inhibitor monotherapy (cohort 1) exhibited the longest median rwOS associated with index therapy (9.18 mo) compared with the other cohorts. An earlier case series indicated that patients with advanced or metastatic NSCLC previously treated with immune checkpoint inhibitors may respond well to subsequent lines of chemotherapy, particularly platinum-based chemotherapy.[11] Interestingly, patients treated with a VEGFi plus chemotherapy did better, with a survival identical to that expected in the first line. Another weakness of this work is the absence of correlative data. We are unable to distinguish a biological effect of PD-L1 expression and VEGF therapy after PD-1/PD-L1 blockade versus patient selection. Regardless, we expect that trial patients are more likely to be fit and more likely to receive more aggressive subsequent therapies, and we propose that a 12.5-month survival might be a meaningful threshold for null hypotheses in future trials of this population. In contrast, patients treated with PD-1/PD-L1 combination therapy had more homogeneous survival outcomes with index therapies, likely reflecting more limited efficacy of available options in this setting. Our analysis found that some patients in each cohort also received PD-1/PD-L1 as their index therapy. It should be noted that disease progression was not a requirement for line of therapy advancement in this analysis; therefore, we conducted a post hoc analysis to understand this pattern. Results from a post hoc analysis among patients being subsequently treated with PD-1/PD-L1 inhibitor revealed that some patients may have added an agent to their PD-1/PD-L1 monotherapy that was after the line of therapy advancement rule regarding addition of an antineoplastic agent after 28 days of PD-1/PD-L1 initiation. In addition, some patients received the same PD-1/PD-L1 at initial treatment and at the index date, indicating that there may have been a gap in therapy. We hypothesize that this gap could have been due to a positive (e.g., patient benefit) or negative (e.g., toxicity) outcome. Thus, due to the definition of index therapy criteria within our study, we are limited on further interpretation of these data.

Beyond those already discussed, additional limitations are associated with retrospective analysis and interpretation of data captured from health records. These include variability in reporting, data entry and reporting errors, missing data, and unmeasured confounding covariates as potential sources of bias. In addition, the reporting of disease progression in EHRs is not standardized like, for example, the Response Evaluation Criteria in Solid Tumors used to estimate treatment response and disease progression in clinical trials. Other limitations include the fact that treatment selection is largely subjective and is based on physician decision as opposed to strict eligibility criteria defined in clinical trial protocols; this may confound index therapy selection and prevent comparisons across groups. Censoring may have also resulted in rwOS being overestimated in some groups. Although we are hopeful that these findings offer a glimpse into real-world treatment patterns and have utility in decision-making in the clinic and in clinical trial design, we caution against overinterpretation or comparison with large, randomized trials. Importantly, the findings of this study remain relevant, as they provide data on the efficacy of chemotherapy in the post–PD-1/PD-L1 setting.

In conclusion, patients with mNSCLC treated with PD-1/PD-L1 are administered a range of index therapy regimens in later lines of therapy. Although platinum-based chemotherapy alone or in combination with bevacizumab (for nonsquamous NSCLC) is recommended as second-line therapy after PD-1/PD-L1 monotherapy and is associated with improved clinical outcomes, this approach was not universally followed in this study population. Interestingly, this analysis of real-world evidence suggests that within the current existing armamentarium of approved therapeutics, the choice of subsequent treatment may have limited effects on overall survival, even though the VEGFi combination with chemotherapy had a better signal and may be worth investigating further in a randomized, controlled setting.

CRediT Authorship Contribution Statement

Savreet Bains: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Anu Kalsekar: Conceptualization, Funding acquisition, Investigation, Supervision, Writing - review & editing.

Katayoun I. Amiri: Conceptualization, Formal analysis, Writing - review & editing.

Jared Weiss: Conceptualization, Funding acquisition, Writing - original draft, Writing - review & editing.

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