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Research Article

PD-L1 Testing, Treatment Patterns, and Clinical Outcomes Among Patients with Metastatic NSCLC at an Academic Medical Center, 2017–2021

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ABSTRACT

Introduction: Targeted therapies and immune checkpoint inhibitors (ICIs) have revolutionized the management of metastatic non–small cell lung cancer (NSCLC) over the past decade. **Methods:** This single-center observational study was conducted to describe programmed death-ligand 1 (PD-L1) testing, choice of therapy, and outcomes for adult patients with stage IV NSCLC initiating first-line therapy from 2017 through 2020, with follow-up through June 2021. Patient characteristics and study assessments were described according to four histomolecular subtypes,

defined by histologic characteristics and availability of standard-of-care therapies for molecular subgroups at the time of study conduct. **Results:** Of 507 eligible patients with metastatic NSCLC, 85 (17%) had squamous NSCLC; 288 (57%) had nonsquamous NSCLC with no actionable genomic alteration; 44 (9%) had nonsquamous NSCLC with *KRAS* G12C mutation; and 90 (18%) had nonsquamous NSCLC with *ROS1*, *BRAF* V600E, *EGFR* exon 20 insertion, or *RET* or *NTRK* genomic alteration. Most tumors were PD-L1 tested. After excluding 40 patients whose PD-L1 testing status was unknown, all but 55 tumors (12%) were tested for PD-L1 expression, and the percentages tested rose from 86% in 2017 to 100% in 2020. From 27% of nonsquamous NSCLC with no actionable genomic alteration to 46% of *KRAS* G12C-mutated NSCLC had PD-L1 expression $\geq$ 50%. Use of chemotherapy decreased and use of ICI-chemotherapy combinations increased from 2017 to 2020. In the squamous NSCLC group, single or combination chemotherapy was administered most commonly (42%), whereas ICI-chemotherapy combinations were the most common first-line regimens in the three nonsquamous NSCLC histomolecular groups. For patients with NSCLC and no actionable genomic alterations, ICI-chemotherapy combinations were the most common regimens in 2018–2020 in all but the PD-L1 $\geq$ 50% category, for whom ICI monotherapy was most common every year except 2020. Median overall survival was 25.0 months (95% CI, 19.1–28.3) for all patients, and, by histomolecular cohort, 14.3 months for squamous NSCLC, 25.3 months for nonsquamous NSCLC with no actionable genomic alteration, not reached for *KRAS* G12C-mutated NSCLC, and 27.7 months for nonsquamous NSCLC with other genomic alterations. **Conclusion:** Study findings highlight the increased use of PD-L1 testing over the years from 2017 to 2020 and recent changes in therapy, with decreased use of chemotherapy and increased use of ICI-chemotherapy combinations during the study in each histomolecular group. Moreover, we observed improvements in survival for patients with metastatic NSCLC relative to historical real-world data.

Keywords: stage IV non–small cell lung cancer, immune checkpoint inhibitors, overall survival, PD-L1 expression, targeted therapy

INTRODUCTION

Advances in targeted therapies for non–small cell lung cancer (NSCLC) with genomic tumor alterations, and the introduction of immune checkpoint inhibitors (ICIs) used as monotherapy or as part of combination therapy, have led to changes in the therapeutic landscape for treatment-naïve advanced and metastatic NSCLC and contributed to substantial improvements in clinical outcomes over the past decade.[1–7] The primary goals of systemic therapy in patients with metastatic NSCLC are to reduce the symptom burden from cancer, delay the progression of symptoms, and improve survival while maintaining quality of life.

With these changes in the treatment paradigm for metastatic NSCLC, there is a need to understand how the emergence of the newer immunotherapy data has influenced physician behavior, both with regard to ordering and interpreting programmed death-ligand 1 (PD-L1) tests for the different histomolecular subtypes of NSCLC and choosing therapy based on test results. In addition, an understanding is needed of contemporary clinical outcomes and symptom improvement for patients with NSCLC treated, not in a clinical trial, but in the real-world clinical setting with attendant constraints on time and finances.

The primary objectives of this observational study were to examine—by histomolecular category of metastatic NSCLC—the PD-L1 testing patterns, choices of treatment regimens by PD-L1 status, and utilization of ICI therapy. In addition, we aimed to capture the duration of ICI therapy and determine survival rates by type of treatment, PD-L1 status, and histomolecular categories of metastatic NSCLC. The secondary objectives to describe patient-reported outcomes for metastatic NSCLC will be reported separately. Here we report the findings for PD-L1 testing, first-line treatment patterns, and clinical outcomes after first-line therapy initiation for patients with metastatic NSCLC at an academic medical center from 2017 to 2021.

METHODS

Patients and Study Design

This was an observational single-center study. Patients were identified among those initiating first-line palliative systemic therapy for advanced NSCLC at The University of Texas MD Anderson Cancer Center (MDACC) from January 1, 2017, to December 31, 2020. Eligible patients consented in accordance with the protocol for the MDACC Institutional Review Board (PA13-0589: GEMINI-Moonshot Project: A prospective database for patients with lung cancer incorporating collection of tissue and clinical information). Patient demographics, clinical characteristics, treatment information, survival data, and tumor molecular profiles were collected by chart abstraction from the GEMINI database. We have followed the guidelines of the STROBE initiative (STrengthening the Reporting of OBservational studies in Epidemiology) for reporting study results.

Eligibility criteria included patients 18 years and older with a histologically or cytologically confirmed diagnosis of metastatic (stage IV) NSCLC who initiated first-line systemic therapy for metastatic NSCLC during the 4-year

eligibility period (2017–2020), excluding those enrolled in an immunotherapy-based clinical trial for first-line therapy. Patients who came to MDACC exclusively for consultation purposes were also excluded. Study follow-up was conducted through June 30, 2021, thereby ensuring a minimum of 6 months' follow-up after first-line therapy initiation. Patients who subsequently enrolled in a clinical trial of second-line or later therapy remained in this observational study, with continued follow-up.

Clinical Assessments

We evaluated patient demographic and clinical characteristics overall and grouped by four histomolecular categories of NSCLC, defined by histologic characteristics and availability of standard-of-care therapies for molecular subgroups at the time of study conduct: (1) squamous cell carcinoma; (2) nonsquamous cell carcinoma with no actionable tumor genomic alteration and excluding patients who received any tyrosine kinase inhibitor (TKI); (3) nonsquamous cell carcinoma with a *KRAS* G12C mutation; and (4) nonsquamous cell carcinoma with any of five other actionable genomic alterations (*ROS1* translocation, *BRAF* V600E mutation, *EGFR* exon 20 insertion mutation, *RET* or *NTRK* fusion).

The patterns of testing for PD-L1 expression were examined by histomolecular category of NSCLC, and we tabulated PD-L1 expression levels by histomolecular category and by treatment regimen. First-line treatment regimens were categorized as ICI monotherapy (pembrolizumab, nivolumab, and atezolizumab), ICI combination therapy (ipilimumab plus nivolumab), ICI plus chemotherapy with or without biologics (e.g., carboplatin-pemetrexed-pembrolizumab or platinum-taxane-atezolizumab with bevacizumab), single agent or combination chemotherapy (e.g., docetaxel or platinum plus docetaxel); TKI, or Other (e.g., bevacizumab or other angiogenesis inhibitor; Supplemental Table S1, available online).

For all patients, we determined overall survival (OS), defined as the time from first-line therapy initiation to death from any cause. Vital status was determined both by reviewing medical record data every 6 months until 6 months after data cutoff and, for patients who were lost to follow-up, by performing a database search using online death registries. Real-world progression-free survival (rwPFS) was defined as the time from first-line therapy initiation to documented clinical disease progression or death from any cause, whichever occurred first. In addition, for patients who received ICI-containing regimens, we determined real-world time on treatment (rwToT), defined as the length of time from the date the patient initiated treatment with an ICI to the date the patient discontinued the treatment (last administration of the ICI-containing regimen). Discontinuation was defined as initiating a subsequent systemic therapy after the initial ICI-containing regimen, a gap of > 120 days with no systemic therapy after the last administration, or having a date of death while on the ICI-containing regimen. Patients with no discontinuation date were censored at their last known ICI use.

The end of patient follow-up was defined as the earliest date among death date, last contact date, or the end of the study (June 30, 2021). Patients were identified as lost to follow-up if no communication occurred with MDACC health care providers for more than 12 months before data cutoff, and for these patients, a database search was performed using online death registries before data lock. End of patient follow-up was the analytically defined data cutoff for retrospective data collection (chart review).

Statistical Analyses

Descriptive analyses were conducted for patient characteristics, PD-L1 testing patterns, and treatment patterns, with continuous variables described using the mean, SD, median, IQR, and/or range, as appropriate, and categorical variables described using frequency and proportions. The Kaplan-Meier method was used to estimate OS and rwPFS by NSCLC histomolecular category, first-line treatment category, PD-L1 expression status, Eastern Cooperative Oncology Group performance status (ECOG PS), and age (< 75 years or ≥ 75 years). In addition, the Kaplan-Meier method was used to estimate rwToT for the ICI-containing regimens, namely, ICI monotherapy, ICI combination therapy, and ICI plus chemotherapy.

This descriptive study included all eligible patients. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc.) and R package (version 4.2.1, R Core Team, 2022). No changes in study analyses were made secondary to the COVID-19 pandemic.

RESULTS

Patients

Of 723 patients with stage IV NSCLC who met initial eligibility criteria and consented to study participation, 507 patients met all eligibility criteria (Supplemental Fig. S1). Among these 507 patients, 85 (17%) had squamous NSCLC, 288 (57%) had nonsquamous NSCLC with no actionable genomic alteration, 44 (9%) had nonsquamous NSCLC with *KRAS* G12C mutation, and 90 (18%) had nonsquamous NSCLC with one of the five other actionable genomic alterations (details in the Methods section). First-line therapy was initiated by 177 patients (35%) in 2017, 144 (28%) in 2018, 121 (24%) in 2019, and 65 (13%) in 2020 (Table 1).

The median age at first-line initiation was 65 years overall (range, 26–91 years), and 77 patients (15%) were ≥ 75 years old. A total of 280 patients were men (55%) and 413 patients (82%) were White, 56 (11%) were Black or African American, and 18 (4%) were of Asian race. Table 1 depicts patient characteristics overall and by histomolecular group. Patients in the group with one of five genomic alterations tended to be younger and more

Table 1. Patient demographic and clinical characteristics overall and by histomolecular group

Characteristic	NSCLC Histomolecular Group				All Patients (*N* = 507)
	Squamous (*n* = 85)	Nonsquamous, No Driver (*n* = 288)	Nonsquamous, *KRAS* G12C (*n* = 44)	Nonsquamous, Other Driver (*n* = 90)	
Year of 1L initiation					
2017	32 (37.6)	103 (35.8)	14 (31.8)	28 (31.1)	177 (34.9)
2018	22 (25.9)	75 (26.0)	11 (25.0)	36 (40.0)	144 (28.4)
2019	18 (21.2)	72 (25.0)	11 (25.0)	20 (22.2)	121 (23.9)
2020	13 (15.3)	38 (13.2)	8 (18.2)	6 (6.7)	65 (12.8)
Age, y, median (range)	67 (33–85)	66 (26–91)	66 (38–82)	60 (36–82)	65 (26–91)
Age group					
< 75 years	68 (80.0)	243 (84.4)	37 (84.1)	82 (91.1)	430 (84.8)
≥ 75 years	17 (20.0)	45 (15.6)	7 (15.9)	8 (8.9)	77 (15.2)
Sex, male	54 (63.5)	166 (57.6)	22 (50.0)	38 (42.2)	280 (55.2)
Race					
White	62 (72.9)	237 (82.3)	40 (90.9)	74 (82.2)	413 (81.5)
Black or African American	17 (20.0)	29 (10.1)	2 (4.5)	8 (8.9)	56 (11.0)
Asian	3 (3.5)	9 (3.1)	1 (2.3)	5 (5.6)	18 (3.6)
Other	3 (3.5)	13 (4.5)	1 (2.3)	3 (3.3)	20 (3.9)
Smoking status[a]					
Current smoker	10 (13.3)	41 (15.8)	8 (22.2)	8 (9.4)	67 (14.7)
Former smoker	54 (72.0)	175 (67.6)	28 (77.8)	35 (41.2)	292 (64.2)
No history of smoking	11 (14.7)	43 (16.6)	0	42 (49.4)	96 (21.1)
Not recorded	10	29	8	5	52
ECOG performance status[a]					
0–1	20 (62.5)	101 (78.9)	18 (72.0)	26 (70.3)	165 (74.3)
2	8 (25.0)	16 (12.5)	7 (28.0)	9 (24.3)	40 (18.0)
3	4 (12.5)	11 (8.6)	0	2 (5.4)	17 (7.7)
Unknown	53	160	19	53	285
Stage at initial diagnosis[a]					
Stage I–III	18 (21.4)	25 (8.8)	12 (27.9)	9 (10.0)	64 (12.7)
Stage IV	66 (78.6)	260 (91.2)	31 (72.1)	81 (90.0)	438 (87.3)
PD-L1 expression[a]					
< 1%	16 (23.2)	79 (35.1)	4 (10.8)	23 (30.3)	122 (30.0)
1–49%	29 (42.0)	86 (38.2)	16 (43.2)	32 (42.1)	163 (40.0)
≥ 50%	24 (34.8)	60 (26.7)	17 (46.0)	21 (27.6)	122 (30.0)
Not tested	8	36	2	9	55[b]
Unknown	8	27	5	5	45[b]

Data are *n* (%) unless otherwise noted. Percentages may not add up to 100 because of rounding.
[a]Percentages for smoking status, ECOG performance status, stage at initial diagnosis, and PD-L1 expression are calculated for patients with known values. Stage at initial diagnosis was not recorded for five patients.
[b]No PD-L1 test results were available for 100 patients, including 55 patients (10.8%) whose tumors were not tested for PD-L1 expression, 40 (7.9%) with unknown testing status, and 5 (1.0%) with unavailable test results.
1L: first-line therapy; driver: actionable tumor genomic alteration; ECOG: Eastern Cooperative Oncology Group; PD-L1: programmed death-ligand 1.

often female than those in the other three groups. The percentage of Black/African American patients ranged from 5% among those with *KRAS* G12C-mutated nonsquamous cell carcinoma to 20% among those with squamous NSCLC.

Of the 222 patients (44%) with recorded performance status, most had ECOG PS of 0 or 1 ($n = 165$; 74%). The percentage with ECOG PS of 0 or 1 ranged from 63% of patients with squamous NSCLC to 79% with nonsquamous NSCLC with no actionable genomic alteration (Table 1). Among 44 patients with *KRAS* G12C-mutated nonsquamous cell carcinoma, the *KRAS* mutation was observed most frequently in adenocarcinomas (39 patients; 89%), in addition to one patient with adenosquamous cell carcinoma, two patients with large cell neuroendocrine carcinoma, and two patients with non–small cell carcinoma not otherwise specified.

Testing for PD-L1 Expression

Immunohistochemistry (IHC) testing for tumor PD-L1 expression was conducted for most patients during the study (Table 1), and the percentages tested rose from 86% in 2017 to 100% in 2020. No PD-L1 test results were available for 100 patients, including 55 patients (11%) whose tumors were not tested for PD-L1 expression, 40 (8%) with unknown testing status, and 5 (1%) with unavailable test results. More than 95% of the PD-L1 tests with recorded assay information used

the monoclonal mouse anti-PD-L1 clone 22C3 assay (data not shown).

The reasons for lack of PD-L1 testing, when known, were reported as either not enough tissue ($n = 31$; 61%) or no request from the physician ($n = 20$; 39%). The greatest percentage of patients with unknown PD-L1 expression (tumor not tested or unknown results) were those with nonsquamous NSCLC with no actionable genomic alteration (63 of 288, 22%; Table 1).

The IHC results for PD-L1 expression differed among the four histomolecular groups, with high expression (PD-L1 $\geq$ 50%) ranging from 27% among patients with nonsquamous NSCLC with no actionable genomic alteration to 46% of patients with *KRAS* G12C mutation (Table 1). Supplemental Table S2 depicts PD-L1 expression by histopathology, and Supplemental Table S3 depicts PD-L1 expression by patient characteristics.

Treatment Patterns

Overall, the most common first-line regimen was ICI plus chemotherapy (46%), followed by single/combination chemotherapy (28%), with ICI monotherapy administered to 19% of patients (Fig. 1A). The most common first-line regimens varied by histomolecular group and clinicopathological characteristics, as depicted in Figure 1A and Table 2.

In the squamous NSCLC group, single or combination chemotherapy was administered most commonly (42%), followed by ICI-chemotherapy combinations (26%) and ICI monotherapy (25%). Monotherapy with an ICI was most often utilized for tumors with PD-L1 expression $\geq$ 50%, and single or combination chemotherapy was most frequently selected for squamous tumors with PD-L1 expression $<$ 50% (Table 2). The ICI-chemotherapy combinations were the most common first-line regimens in the three nonsquamous NSCLC histomolecular groups: nonsquamous NSCLC with no actionable genomic alteration (51%), with *KRAS* G12C mutation (52%), and with one of the five other genomic alterations (47%; Fig. 1A).

First-line regimens administered by histomolecular category changed by study year, with decreasing use of chemotherapy and increasing use of ICI-chemotherapy combinations from 2017 to 2020 (Table 3). Similarly, the use of chemotherapy decreased over time in each PD-L1 expression category among patients with NSCLC and no *EGFR*, *ALK*, or *ROS1* genomic alterations, whereas ICI-chemotherapy combinations were the most common regimens in 2018–2020 in all but the PD-L1 $\geq$ 50% category, for whom ICI monotherapy was most common every year except 2020 (Table 4). A total of 109 patients (21%) received a second-line regimen during the study, most commonly single or combination chemotherapy (34%), ICI monotherapy (32%), a TKI (13%), or an ICI-chemotherapy combination (12%; Fig. 1B).

Clinical Outcomes

At the time of data cutoff (June 30, 2021), 226 patients (45%) had died, 33 (7%) were lost to follow-up, and 245 (49%) were alive, including 219 (43%) with still-present disease, 21 (4%) with complete clinical and radiological response to therapy, and 5 (1%) with unknown disease status.

The median OS in the full study population was 25.0 months (95% CI, 19.1–28.3). Median OS by histomolecular cohort was 14.3 months for squamous NSCLC, 25.3 months for nonsquamous NSCLC with no genomic alteration, not reached (NR) for *KRAS* G12C-mutated NSCLC, and 27.7 months for nonsquamous NSCLC with other driver mutations (95% CI and details in Table 5). Median OS was 29.9 months for patients with ECOG PS of 0 or 1, and median OS was 15.0 months for those with ECOG PS of 2, and 10.8 months for the 17 patients with ECOG PS of 3. Among 427 patients younger than 75 years, the median OS was 25.8 months, and among 77 patients who were 75 years or older, median OS was 24.7 months (Table 5). The median rwPFS in the full study population was 8.3 months (95% CI, 6.7–10.2; Table 5).

Among patients who received an ICI-containing regimen, the median rwToT was 9.0 months (95% CI, 6.7–11.7) with ICI plus chemotherapy ($n = 232$), 14.5 months (95% CI, 7.0–NR) with ICI monotherapy ($n = 93$), and NR (95% CI, 0.4–NR) with ICI combination therapy (ipilimumab-nivolumab; $n = 8$).

DISCUSSION

In this large observational study at an academic center, we retrospectively studied 507 patients with treatment-naïve stage IV NSCLC to describe their demographic and clinical characteristics and their physicians' choices regarding PD-L1 testing and treatment patterns, together with outcomes after first-line therapy initiation from 2017 through 2020. We observed that PD-L1 testing was conducted for most patients and gradually rose during the study from 86% of patients with recorded test information in 2017 to 100% in 2020, although there was variability among NSCLC histomolecular groups in the percentage tested. First-line regimens changed over time, and the treatment patterns and rwPFS and OS outcomes also varied by histomolecular group, as further discussed later in this article. Histomolecular subtypes appeared to influence patterns of first-line treatment regimens, although the study was not powered for formal statistical comparisons.

We established the four histomolecular NSCLC categories, including squamous NSCLC and three categories of nonsquamous NSCLC, to divide patients into subgroups based on tumor biology and availability of alternative systemic therapy options. In 2016, when this study was conceptualized, the US Food and Drug Administration (FDA)–approved molecular targeted

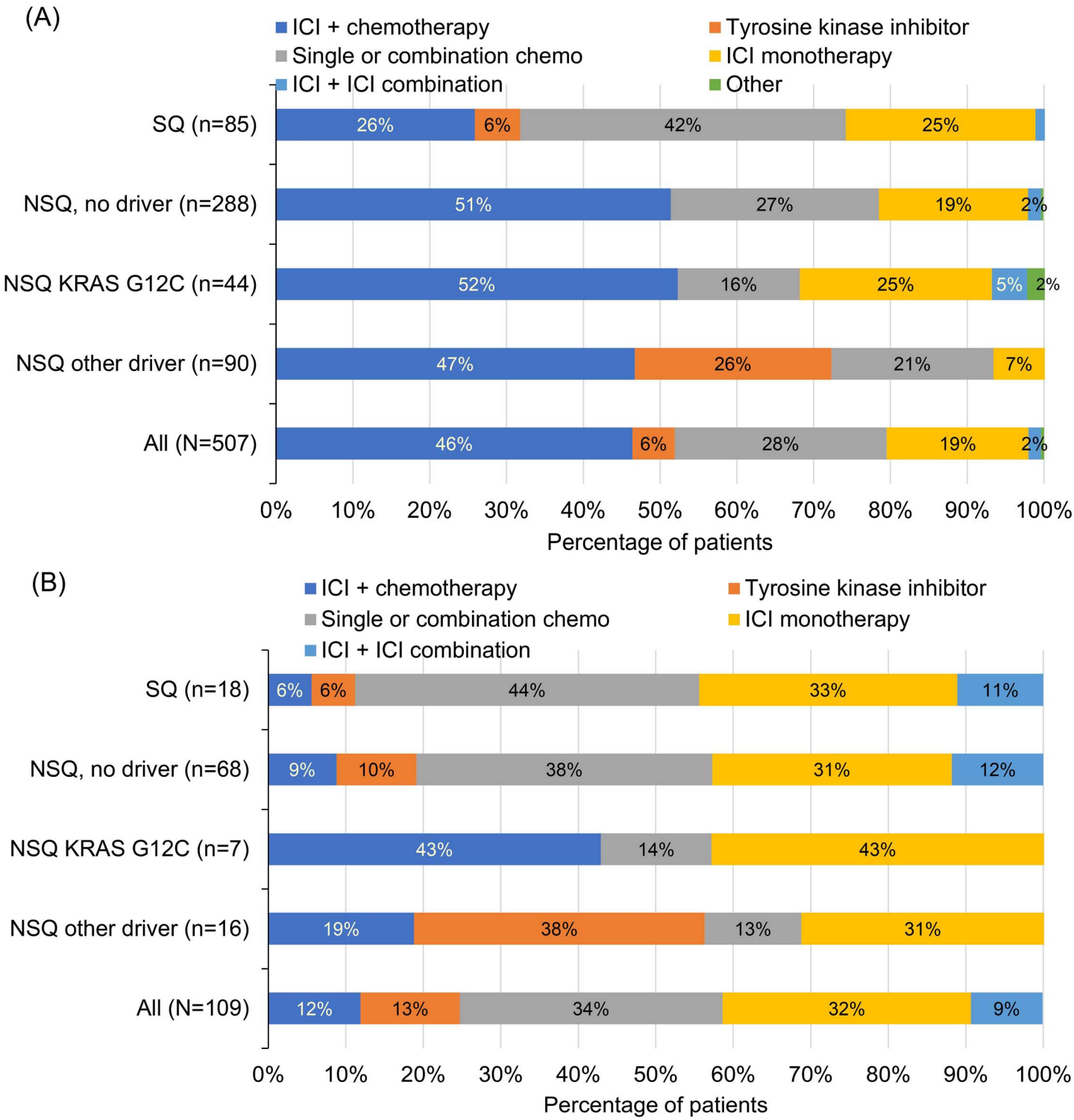

Figure 1. (A) First-line and (B) second-line treatment regimens overall and by histomolecular group.

chemo: chemotherapy; driver: actionable tumor genomic alteration; ICI: immune checkpoint inhibitor; NSQ: nonsquamous; SQ: squamous.

therapies were limited to TKIs for tumors harboring *EGFR* exon 19 deletions and exon 21 L858R point mutations or *ALK* translocation (fusion). These genomic alterations are most commonly observed in nonsquamous cell carcinomas, and are found uncommonly in squamous NSCLC but usually with response rates to targeted therapies that are lower and short-lived.[8] Patients with metastatic NSCLC with *EGFR* exon 20 insertion mutations were included in the fourth histomolecular group because these tumors have a different response dynamic, with no clinical benefit accruing from traditional epidermal growth factor receptor (EGFR)-targeting

Table 2. First-line treatment regimens for each histomolecular group by age, sex, ECOG performance status, and PD-L1 expression

Clinicopathologic Variables by Histomolecular Cohort	Total, *N*	ICI + Chemo (*n* = 235)	Single or Combination Chemo (*n* = 140)	ICI Monotherapy (*n* = 94)	TKI (*n* = 28)	ICI + ICI Combination (*n* = 8)
Squamous, *n* (%)	85	22 (25.9)	36 (42.4)	21 (24.7)	5 (5.9)	1 (1.2)
Age						
< 75 years	68	18 (26.5)	29 (42.6)	15 (22.1)	5 (7.4)	1 (1.5)
≥ 75 years	17	4 (23.5)	7 (41.2)	6 (35.3)	0	0
Sex						
Female	31	9 (29.0)	13 (41.9)	5 (16.1)	3 (9.7)	1 (3.2)
Male	54	13 (24.1)	23 (42.6)	16 (29.6)	2 (3.7)	0
ECOG performance status[a]						
0–1	20	3 (15.0)	13 (65.0)	2 (10.0)	2 (10.0)	0
2	8	4 (50.0)	3 (37.5)	0	1 (12.5)	0
3	4	2 (50.0)	0	2 (50.0)	0	0
PD-L1 expression[a]						
< 1%	16	3 (18.8)	12 (75.0)	1 (6.3)	0	0
1–49%	29	12 (41.4)	9 (31.0)	5 (17.2)	2 (6.9)	1 (3.4)
≥ 50%	24	3 (12.5)	5 (20.8)	14 (58.3)	2 (8.3)	0
Nonsquamous, no driver, *n* (%)	288	148 (51.4)	78 (27.1)	56 (19.4)	1 (0.3)[b]	5 (1.7)
Age						
< 75 years	243	124 (51.0)	72 (29.6)	43 (17.7)	1 (0.4)[b]	3 (1.2)
≥ 75 years	45	24 (53.3)	6 (13.3)	13 (28.9)	0	2 (4.4)
Sex						
Female	122	67 (54.9)	29 (23.8)	24 (19.7)	0	2 (1.6)
Male	166	81 (48.8)	49 (29.5)	32 (19.3)	1 (0.6)[b]	3 (1.8)
ECOG performance status						
0–1	101	42 (41.6)	29 (28.7)	27 (26.7)	1 (1.0)[b]	2 (2.0)
2	16	7 (43.8)	9 (56.3)	0	0	0
3	11	6 (54.5)	4 (36.4)	1 (9.1)	0	0
PD-L1 expression						
< 1%	79	45 (57.0)	26 (32.9)	6 (7.6)	0	2 (2.5)
1–49%	86	49 (57.0)	25 (29.1)	9 (10.5)	1 (1.2)[b]	2 (2.3)
≥ 50%	60	19 (31.7)	6 (10.0)	35 (58.3)	0	0
Nonsquamous, *KRAS* G12C, *n* (%)	44	23 (52.3)	7 (15.9)	11 (25.0)	1 (2.3)[b]	2 (4.5)
Age						
< 75 years	37	20 (54.1)	7 (18.9)	7 (18.9)	1 (2.7)[b]	2 (5.4)
≥ 75 years	7	3 (42.9)	0	4 (57.1)	0	0
Sex						
Female	22	9 (40.9)	3 (13.6)	7 (31.8)	1 (4.5)[b]	2 (9.1)
Male	22	14 (63.6)	4 (18.2)	4 (18.2)	0	0
ECOG performance status						
0–1	18	10 (55.6)	3 (16.7)	3 (16.7)	0	2 (11.1)
2	7	3 (42.9)	2 (28.6)	2 (28.6)	0	0
PD-L1 expression						
< 1%	4	2 (50.0)	2 (50.0)	0	0	0
1–49%	16	9 (56.3)	4 (25.0)	1 (6.3)	0	2 (12.5)
≥ 50%	17	6 (35.3)	0	10 (58.8)	1 (5.9)[b]	0
Nonsquamous, other driver, *n* (%)	90	42 (46.7)	19 (21.1)	6 (6.7)	23 (25.6)	0
Age						
< 75 years	82	39 (47.6)	16 (19.5)	6 (7.3)	21 (25.6)	0
≥ 75 years	8	3 (37.5)	3 (37.5)	0	2 (25.0)	0

Table 2 continues on next page

Table 2. Continued

Clinicopathologic Variables by Histomolecular Cohort	Total, *N*	ICI + Chemo (*n* = 235)	Single or Combination Chemo (*n* = 140)	ICI Monotherapy (*n* = 94)	TKI (*n* = 28)	ICI + ICI Combination (*n* = 8)
Sex						
Female	52	25 (48.1)	9 (17.3)	4 (7.7)	14 (26.9)	0
Male	38	17 (44.7)	10 (26.3)	2 (5.3)	9 (23.7)	0
ECOG performance status						
0–1	26	12 (46.2)	4 (15.4)	2 (7.7)	8 (30.8)	0
2	9	4 (44.4)	2 (22.2)	1 (11.1)	2 (22.2)	0
3	2	1 (50.0)	0	1 (50.0)	0	0
PD-L1 expression						
< 1%	23	11 (47.8)	8 (34.8)	0	4 (17.4)	0
1–49%	32	15 (46.9)	6 (18.8)	0	11 (34.4)	0
≥50%	21	11 (52.4)	2 (9.5)	6 (28.6)	2 (9.5)	0

Row percentages were used in constructing this table.
Data are *n* (%), and percentages may not add up to 100 because of rounding.
[a]Only patients with known ECOG performance status and PD-L1 expression data are included in the table.
[b]These two single patients in nonsquamous/no driver and nonsquamous/*KRAS* cohorts received an "other" therapy (not a TKI).
1L: first-line therapy; Chemo: chemotherapy; driver: actionable tumor genomic alteration; ECOG: Eastern Cooperative Oncology Group; ICI: immune checkpoint inhibitor; PD-L1: programmed death-ligand 1; TKI: tyrosine kinase inhibitor.

TKIs.[9] Moreover, EGFR exon 20 targeted investigational therapies such as mobocertinib (withdrawn in October 2023) and amivantamab, although off-label during the study period, were available for a patient subset and given in the setting of clinical trials. During the study period, a number of new targeted therapies were FDA approved for tumor genomic aberrations, including for NSCLC with *ROS1* translocation (fusion), *BRAF* V600E mutation, *RET* fusion, and *NTRK* fusion, assigned to the fourth histomolecular group.[4] Targeted therapies for previously treated *KRAS* G12C-mutated NSCLC were approved after the study eligibility period (in May 2021 and December 2022).

For tumors with no actionable genomic alterations, we observed that utilization of ICI-chemotherapy combinations increased during the study overall and in all PD-L1 expression groups, whereas we noted an overall decreasing use of single or combination chemotherapy over time in all PD-L1 expression groups (see Table 4). The use of ICI monotherapy was greatest in all study years except 2020 for high PD-L1–expressing tumors (PD-L1 tumor proportion score $\geq$ 50%) without actionable alterations, with relatively low use for those with PD-L1 1–49%, ranging from 3–21% of patients in a given year. Over the 4 study years, we noted a possible trend of decreasing utilization of ICI monotherapy, which could be attributable to decreased patient numbers in 2020 or secondary to an increase at our academic center in ICI-based clinical trial options that enrolled immunotherapy-naïve patients, who were thus excluded from this observational study.

Most patients with nonsquamous cell carcinoma with *KRAS* G12C mutation had available PD-L1 test results (n = 37; 84%), and almost half of the 37 patients (46%) had high-expressing tumors (PD-L1 expression of $\geq$ 50%). Half of patients in this group received first-line ICI monotherapy in 2017; by 2020, all received first-line ICI-chemotherapy combinations.

A retrospective study of survival after first-line therapy for stage IV NSCLC without *EGFR* or *ALK* genomic alterations in 2012 to 2015, before immunotherapies were available, found that median OS was 8.5 months for squamous and 10.0 months for nonsquamous NSCLC.[10] In the present study, the median OS was 14.3 months for squamous NSCLC and 25.3 months for nonsquamous NSCLC without actionable genomic alterations, a finding that highlights the improvement in life expectancy for patients with metastatic NSCLC who are treated with novel therapies. Moreover, this finding is consistent with ICI studies regarding lower survival rates for squamous than nonsquamous NSCLC histology,[11–13] including the updated reports of combination pembrolizumab plus chemotherapy for squamous NSCLC in KEYNOTE-407 (median OS, 17.2 months; 95% CI, 14.4–19.7) and nonsquamous NSCLC in KEYNOTE-189 (19.4 months; 95% CI, 15.7–23.4).[14,15] With ICI monotherapy, administered mostly to patients with high PD-L1-expressing

Table 3. First-line treatment regimens by year for each histomolecular group

Clinicopathologic Variables by Histomolecular Cohort	Total *N*	ICI + Chemo (*n* = 235)	Single or Combination Chemo (*n* = 140)	ICI Monotherapy (*n* = 94)	TKI (*n* = 28)	ICI + ICI Combination (*n* = 8)
Squamous						
Year of 1L initiation, *n*	85	22	36	21	5	1
2017	32	0	18 (56.3)	10 (31.3)	4 (12.5)	0
2018	22	3 (13.6)	14 (63.6)	4 (18.2)	0	1 (4.5)
2019	18	10 (55.6)	2 (11.1)	5 (27.8)	1 (5.6)	0
2020	13	9 (69.2)	2 (15.4)	2 (15.4)	0	0
Nonsquamous, no driver						
Year of 1L initiation, *n*	288	148	78	56	1[a]	5
2017	103	28 (27.2)	46 (44.7)	28 (27.2)	1 (1.0)[a]	0
2018	75	48 (64.0)	19 (25.3)	7 (9.3)	0	1 (1.3)
2019	72	46 (63.9)	8 (11.1)	14 (19.4)	0	4 (5.6)
2020	38	26 (68.4)	5 (13.2)	7 (18.4)	0	0
Nonsquamous, *KRAS* G12C						
Year of 1L initiation, *n*	44	23	7	11	1[a]	2
2017	14	2 (14.3)	5 (35.7)	7 (50.0)	0	0
2018	11	7 (63.6)	1 (9.1)	1 (9.1)	1 (9.1)[a]	1 (9.1)
2019	11	6 (54.5)	1 (9.1)	3 (27.3)	0	1 (9.1)
2020	8	8 (100)	0	0	0	0
Nonsquamous, other driver						
Year of 1L initiation, *n*	90	42	19	6	23	0
2017	28	6 (21.4)	13 (46.4)	3 (10.7)	6 (21.4)	0
2018	36	17 (47.2)	5 (13.9)	3 (8.3)	11 (30.6)	0
2019	20	15 (75.0)	0	0	5 (25.0)	0
2020	6	4 (66.7)	1 (16.7)	0	1 (16.7)	0

Row percentages were used in constructing this table.
Data are *n* (%) unless otherwise noted, and percentages may not add up to 100 because of rounding.
[a]These two single patients in nonsquamous/no driver and nonsquamous/*KRAS* cohorts received an "other" therapy (not a TKI).
1L: first-line therapy; Chemo: chemotherapy; driver: actionable tumor genomic alteration; ICI: immune checkpoint inhibitor; TKI: tyrosine kinase inhibitor.

tumors, the median OS in this study was 35.7 months, which is longer than in the reference KEYNOTE-024 study of pembrolizumab monotherapy (median OS, 26.3 months; 95% CI, 18.3–40.4).[16] Patient selection in the setting of a single-center study may contribute to this difference. In addition, the very high level of PD-L1 expression,[17] more flexible utilization of ICI therapy beyond progression (vs in a clinical trial), particularly in the setting of

Table 4. First-line treatment regimens by year, according to PD-L1 expression, for 365 patients with NSCLC and no *EGFR*, *ALK*, or *ROS1* genomic alteration

PD-L1 by Year	Total *N*	ICI + Chemo	Single or Combination Chemo	ICI Monotherapy	ICI + ICI combination	TKI	Other
PD-L1 < 1%, *n*	107	54	44	7	2	0	0
2017	43	8 (18.6)	29 (67.4)	6 (14.0)	0	0	0
2018	36	21 (58.3)	14 (38.9)	0	1 (2.8)	0	0
2019	19	17 (89.5)	1 (5.3)	0	1 (5.3)	0	0
2020	9	8 (88.9)	0	1 (11.1)	0	0	0
PD-L1 1-49%, *n*	145	80	42	15	5	2	1
2017	53	16 (30.2)	26 (49.1)	8 (15.1)	0	2 (3.8)	1 (1.9)
2018	35	21 (60.0)	11 (31.4)	1 (2.9)	2 (5.7)	0	0
2019	38	30 (78.9)	3 (7.9)	2 (5.3)	3 (7.9)	0	0
2020	19	13 (68.4)	2 (10.5)	4 (21.1)	0	0	0
PD-L1 ≥ 50%, *n*	113	32	13	65	0	2	1
2017	45	7 (15.6)	8 (17.8)	29 (64.4)	0	1 (2.2)	0
2018	29	10 (34.5)	4 (13.8)	14 (48.3)	0	0	1 (3.4)
2019	29	9 (31.0)	0	19 (65.5)	0	1 (3.4)	0
2020	10	6 (60.0)	1 (10.0)	3 (30.0)	0	0	0

All percentages are row percentages.
Data are *n* (%) unless otherwise indicated, and percentages may not add up to 100 because of rounding.
Chemo: chemotherapy; combo: combination; ICI: immune checkpoint inhibitor; PD-L1: programmed death-ligand 1; TKI: tyrosine kinase inhibitor.

Table 5. Kaplan-Meier analyses of OS and rwPFS from first-line therapy initiation: overall and by clinicopathologic variables

Variable	*N* (Event)	Median OS (95% CI), mo	*N* (Event)	Median rwPFS (95% CI), mo
Overall	504 (226)	25.0 (19.1–28.3)	503 (302)	8.3 (6.7–10.2)
By histomolecular cohort				
Squamous	84 (40)	14.3 (11.2–27.3)	84 (50)	7.3 (4.9–11.6)
Nonsquamous, no driver	287 (129)	25.3 (19.1–29.7)	286 (180)	7.5 (5.7–9.0)
Nonsquamous, *KRAS* G12C	43 (16)	NR (18.6–NR)	43 (19)	21.5 (6.7–NR)
Nonsquamous, other driver	90 (41)	27.7 (14.0–NR)	90 (53)	9.9 (6.1–18.3)
By first-line regimen type[b]				
ICI monotherapy	94 (37)	35.7 (24.7–NR)	93 (45)	25.3 (8.4–NR)
ICI + chemotherapy	232 (107)	23.2 (16.9–28.2)	232 (136)	10.5 (8.5–14.3)
Single or combination chemo	140 (66)	18.5 (12.3–25.8)	140 (101)	3.9 (3.4–5.7)
Tyrosine kinase inhibitor	28 (13)	20.0 (10.3–NR)	28 (16)	14.3 (5.7–20.0)
By available ECOG PS[c]				
All patients with ECOG data	220 (91)	27.7 (21.0–38.7)	220 (126)	8.1 (6.0–10.3)
0–1	163 (63)	29.9 (25.3–NR)	163 (92)	8.6 (5.8–17.1)
2	40 (18)	15.0 (7.8–NR)	40 (20)	8.1 (3.2–14.3)
3	17 (10)	10.8 (7.3–24.7)	17 (14)	8.1 (2.1–10.2)
By age				
< 75	427 (191)	25.8 (19.1–29.0)	426 (260)	7.4 (6.0–9.0)
≥ 75	77 (35)	24.7 (14.9–38.5)	77 (42)	11.9 (8.3–25.2)

[a]OS analysis excluded 3 patients with < 0 OS time; and rwPFS analysis excluded 4 patients with < 0 rwPFS time.
[b]Findings by first-line regimen type not reported for eight patients who received ICI+ICI combination and two patients who received "Other" regimen type.
[c]Findings by ECOG PS excluded 284 patients with missing ECOG status in OS and 283 patients with missing ECOG status in rwPFS and rwToT.
chemo: chemotherapy; driver: actionable tumor genomic alteration; ECOG PS: Eastern Cooperative Oncology Group performance status; ICI: immune checkpoint inhibitor; OS: overall survival; NR: not reached; rwPFS: real-world progression-free survival; rwToT: real-world time on treatment.

mixed response,[18] and subsequent clinical trial options in an academic center may improve the outcomes.

Strengths and Limitations

Clinical trials that led to the FDA approvals of ICI therapy for metastatic NSCLC were not specifically designed to exclude older patients; however, older adults were underrepresented in some trials,[19–23] as they are in oncology registration trials in general.[24] This study included 77 patients (15%) who were 75 years or older. In addition, we included 57 patients with ECOG PS of ≥ 2 (26% of those with recorded ECOG PS), patients who would be excluded from most clinical trials. Other strengths of the study are the large patient population (507 patients) and the detailed recording of most patient characteristics and outcomes.

We acknowledge that the study population and practice patterns captured in this study are from one academic cancer center and may not be representative of the US patient population and treatment practices for NSCLC in the United States. Better survival at academic and high-volume facilities has been attributed to more rapid institution of novel treatments than at community practices.[25,26] Therefore, the generalizability of the results may be limited. Another limitation is the small number of patients in certain stratification groups, resulting in wide confidence intervals for estimates generated. Like other observational studies, this study is susceptible to unavailability of important covariates and missing data in medical records, such as ECOG PS, which was missing for more than half (56%) of patients. Radiologic tumor measurement was also unavailable; therefore, estimation of overall response rates and radiologic progression assessments were not feasible. Moreover, patients who were lost to follow-up may have died, which could bias the estimation of OS. To minimize this bias, we reviewed death registries and available electronic medical records throughout our hospital system to capture the most accurate OS information available. Finally, study enrollment fell substantially in 2020, likely because of the COVID-19 pandemic.

CONCLUSION

Targeted therapies and ICIs, particularly inhibitors of the PD-1 axis, have revolutionized the management of metastatic NSCLC over the past decade. This study describes patterns of PD-L1 testing, choice of first-line therapy based on the test results and other clinicopathologic characteristics, and survival outcomes for different histomolecular subtypes of NSCLC. Study findings highlight the increased use of PD-L1 testing over the years from 2017 to 2020 and recent changes in therapy, with decreased use of chemotherapy and increased use of ICI-chemotherapy combinations during the study in each histomolecular group. Moreover, we observed improvements in survival for these patients with metastatic NSCLC relative to historical real-world data. Our findings require validation in multicenter cohorts, together with continued study of real-world testing and treatment patterns

considering the rapidly evolving treatment landscape for metastatic NSCLC.

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Supplemental Material

Supplemental materials are available online with the article.

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