



Characterizing the Shifting Real-World Treatment Landscape by PD-L1 Testing Status and Expression Level in Advanced Non-Small Cell Lung Cancer

Wenzhen Ge · Ning Wu · Ruben G. W. Quek · Jinjie Liu ·
Jean-Francois Pouliot · Hilary Dietz · Jessica J. Jalbert ·
James Harnett · Scott J. Antonia

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ABSTRACT

Introduction: Contemporary real-world data on advanced non-small cell lung cancer (aNSCLC) treatment patterns across programmed cell death-ligand 1 (PD-L1) expression levels and testing status are limited.

Methods: A retrospective cohort was selected of adults newly diagnosed with aNSCLC between January 1, 2018, and July 31, 2021, who initiated first-line treatments, which were described by PD-L1 status and expression levels ($\geq 50\%$, 1–49%, $< 1\%$). Treatment received before and after PD-L1 test results were described for patients initiating first-line treatment before PD-L1 results. For patients who initiated chemotherapy alone before PD-L1 results, the probability of receiving immune checkpoint inhibitors (ICIs) after PD-L1 results was

estimated by PD-L1 level and associated factors were explored.

Results: Among 12,202 patients with aNSCLC initiating first-line treatment [54.7% male, mean (standard deviation) age 69.2 (9.4) years], the most common therapies were ICI-based regimens across PD-L1 levels, and chemotherapy alone among PD-L1-untested patients. Use of chemotherapy alone decreased between 2018 and 2019 and stabilized thereafter, accounting for 21–29% of first-line treatments across PD-L1 levels and 48% of untested patients in 2021. Of 1468 patients initiating first-line treatment before PD-L1 results, treatments remained unchanged in most patients after PD-L1 results. Among patients initiating chemotherapy alone before PD-L1 results, the probability of receiving ICIs within 45 days after test results was 40.5% [95% confidence interval (CI) 31.6–48.3%], 28.6% (95% CI 20.3–36.0%), and 22.9% (95% CI 16.9–28.4%) at PD-L1 $\geq 50\%$, 1–49%, and $< 1\%$, respectively.

Conclusion: While ICI-based regimens accounted for most first-line treatments across PD-L1 levels, chemotherapy alone was initiated in $> 20\%$ of patients tested for PD-L1 and 48% of untested patients in 2021. Patients who initiated chemotherapy alone had a low probability of receiving ICIs after PD-L1 test results. These results highlight the need for understanding the role and timing of PD-L1 test results for informing treatment decisions for patients with aNSCLC.

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W. Ge (✉) · N. Wu · R. G. W. Quek · J.-F. Pouliot ·
J. J. Jalbert · J. Harnett
Regeneron Pharmaceuticals, Inc., 1 Rockwood Road,
Sleepy Hollow, NY 10591, USA
e-mail: wenzhen.ge@regeneron.com

J. Liu
Genesis Research, LLC, Hoboken, NJ, USA

H. Dietz · S. J. Antonia
Center for Cancer Immunotherapy, Duke University
School of Medicine, Durham, NC, USA

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Key Summary Points

Why carry out this study?

To better understand the role of programmed cell death-ligand 1 (PD-L1) testing in the treatment of advanced non-small cell lung cancer and how PD-L1 testing results may inform subsequent treatment.

Since contemporary data on treatment patterns across different levels of PD-L1 expression are limited, this study used a large electronic health record–derived database to characterize the treatment landscape between 2018 and 2021 stratified by PD-L1 expression levels and testing status.

What was learned from the study?

Patterns of first-line treatment of advanced non-small cell lung cancer changed between 2018 and 2019 but subsequently stabilized; observed treatments were generally consistent with guidelines for use of immune checkpoint inhibitors, although in 2021, chemotherapy alone continued to be used in 21–29% of patients across PD-L1 expression levels and in 48% of untested patients.

Most patients who initiated chemotherapy alone before receiving PD-L1 test results did not change treatment after receiving PD-L1 testing results regardless of PD-L1 expression level.

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, and most patients have advanced disease (aNSCLC) at initial diagnosis [1]. Platinum-based doublet chemotherapy was considered the standard of care in patients with aNSCLC who are negative for genomic aberrations including epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) translocation, or C-ROS oncogene 1 (*ROS1*) rearrangement [2–4]. The approval of immunotherapies such as immune checkpoint inhibitors (ICIs) that target programmed cell death-ligand 1 (PD-L1) changed the treatment paradigm for aNSCLC [5–8].

In 2016, the US Food and Drug Administration approved the first ICI as monotherapy for first-line treatment of patients with aNSCLC with PD-L1 expression $\geq 50\%$. The indication was expanded to include patients with aNSCLC and PD-L1 $\geq 1\%$ (2019) or in combination with chemotherapy for those with non-squamous (2017) and squamous (2018) histology regardless of PD-L1 expression levels [9–11]. Current National Comprehensive Cancer Network (NCCN) guidelines for treatment of aNSCLC reflect these changes and recommend ICI-based therapy across all PD-L1 expression levels [12].

Characterizing the treatment landscape advances our understanding of how these therapies are used in real-world clinical settings, and could potentially inform management strategies to enhance patient outcomes. While several studies have reported patterns of first-line treatment for aNSCLC subsequent to ICI approval [13–17], these studies did not stratify by PD-L1 expression level and covered only the initial years after the introduction of ICIs and thus may not reflect contemporary management of patients with aNSCLC. Therefore, the objective of this study was to describe the treatment landscape and trends among patients with aNSCLC initiating first-line treatment across PD-L1 expression levels and those not undergoing PD-L1 testing. An additional objective was to understand the role of PD-L1 test results on treatment patterns by

characterizing treatment changes among patients initiating first-line treatment before obtaining their PD-L1 test results.

METHODS

Study Design

This was a retrospective cohort study of adult patients newly diagnosed with aNSCLC between January 1, 2018, and July 31, 2021, who initiated first-line systemic therapy in the nationwide Flatiron Health de-identified electronic health record (EHR)-derived database. The Flatiron Health EHR database is a large, longitudinal database comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction. During the study period (2018–2021), the de-identified data originated from approximately 280 US cancer clinics (~ 800 sites of care) [18].

The data were already de-identified and subject to obligations to prevent re-identification and protect patient confidentiality. Institutional review board approval of the study protocol for creating the aNSCLC research database was obtained by Flatiron Health before the current study was conducted and included a waiver of informed consent.

Study Populations

The study included patients who had newly diagnosed aNSCLC between January 1, 2018, and July 31, 2021, within the Flatiron Health database; the diagnosis of aNSCLC was confirmed by Flatiron Health review of pathology reports. Patients were also required to be ≥ 18 years old on the diagnosis date and to have initiated first-line systemic treatment within 90 days after the diagnosis date (index date = date of first-line treatment initiation). Patients were excluded if they had a positive biomarker test result for *EGFR*, *ALK*, or *ROS1*, or use of corresponding targeted therapies, or had participated in a clinical trial any time before or within 30 days post-index.

The main cohort consisted of eligible patients who either (1) had a determinable PD-L1 expression level test result before or up to 28 days after first-line systemic therapy initiation or (2) did not have PD-L1 testing or any result within the same window (i.e., untested).

From the main cohort, a sub-cohort of patients was also selected who initiated treatment before receiving PD-L1 testing results to evaluate how PD-L1 results might affect subsequent treatment. These patients were required to have no PD-L1 results before or at initiation of first-line therapy, and valid PD-L1 test results within 28 days after initiation of first-line therapy.

PD-L1 Levels

Among patients with determinable PD-L1 expression levels from a valid PD-L1 test result before or within 28 days of first-line treatment initiation, patients were categorized as having high PD-L1 expression ($\geq 50\%$), low PD-L1 expression (1–49%), or negative for PD-L1 ($< 1\%$ expression). If multiple test results were available, PD-L1 expression level was assigned based on the highest test result.

Treatment Patterns

Lines of therapy (LOTs) were identified using Flatiron Health oncologist-defined rules [19]. Briefly, LOT identification started from the initial aNSCLC diagnosis date, and eligible systemic treatments initiated within 28 days of the first eligible drug episode were considered one LOT. A gap of > 120 days between any two sequential drug episodes caused the LOT number to advance.

Outcomes: First-Line Treatment, Treatment Changes After PD-L1 Test Results

In the main cohort, first-line treatments were classified into platinum-based chemotherapy alone, ICI monotherapy, ICI + platinum-based chemotherapy (ICI + chemotherapy), and other therapies (i.e., any other systemic

treatment that did not fall into the prior categories), regardless of whether patients also received therapy targeting vascular endothelial growth factor. In the sub-cohort, treatment regimens initiated before the test results were compared with the treatment regimen up to 45 days after receiving the PD-L1 test results.

Other Variables

Baseline demographic and clinical characteristics included age at aNSCLC diagnosis, sex (male, female), race and ethnicity (Asian, Black or African American, Hispanic or Latino, White, other race), payer type (commercial, Medicare, Medicaid, other or unknown), histology (non-squamous cell carcinoma, squamous cell carcinoma, NSCLC not otherwise specified), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1, 2–4, unknown), de novo versus recurrent aNSCLC, metastasis to bone (yes, no), metastasis to liver or bile duct (yes, no), and metastasis to brain (yes, no). ECOG performance status was assessed within 90 days before the index date, and the closest value to index date was used when multiple scores were available. Metastasis (bone, liver, brain) was defined as having any diagnosis of secondary malignancy of the corresponding site on or any time before the index date.

Statistical Analysis

Descriptive statistics for baseline characteristics included means, standard deviations (SD), medians, and 25th and 75th percentiles for continuous variables, with number and percentage presented for categorical variables. In the main cohort, demographic and clinical characteristics were described overall, by PD-L1 expression level subgroups (< 1%, 1–49%, \geq 50%), and for those without PD-L1 testing. The sub-cohort was stratified by type of first-line treatment initiated before PD-L1 results and PD-L1 expression levels.

Descriptive analysis of the main cohort consisted of the proportion of patients with each type of first-line treatment stratified by PD-L1 expression level, with further stratification

by index year to characterize changes in the treatment landscape over time. In the sub-cohort, the type of treatment received before PD-L1 results and within 45 days after PD-L1 results was evaluated and stratified by PD-L1 level (< 1%, 1–49%, \geq 50%). Among patients who initiated chemotherapy alone before PD-L1 results, the Kaplan–Meier method was used to estimate the probability and 95% confidence interval (CI) of receiving ICI (either added to chemotherapy or as a switch to monotherapy) after receiving the PD-L1 test results, stratified by PD-L1 expression levels; log-rank tests were used to compare the groups. Cox proportional hazard models were used to derive hazard ratios (HRs) with 95% CIs to evaluate the impact of baseline demographic and clinical characteristics, including PD-L1 expression levels, on the initiation of ICIs by day 45 among patients who initiated chemotherapy alone before receiving PD-L1 test results.

RESULTS

Patient Population

From among the 73,568 patients with NSCLC in the Flatiron Health database at the time of the study, 25,144 adults were newly diagnosed with aNSCLC during the study period, of whom 16,152 initiated first-line systemic treatment within 90 days of their aNSCLC diagnosis and 12,202 of these met all study criteria and were included in the main cohort; 1468 patients from the main cohort met the criteria for sub-cohort analysis (Fig. 1). Patients in the main cohort were primarily male (54.7%), White (66.5%), and had a mean (SD) age of 69.2 (9.4) years (Table 1). The South had the greatest representation (46.0%), and 50.6% of the patients were commercially insured. Diagnosis of aNSCLC was de novo in 75.9% of patients, with most patients having non-squamous cell carcinoma histology (64.6%) and ECOG performance status 0 or 1 (59.1%) (Table 1).

The distribution of patients across the three PD-L1 levels was comparable (23.8–26.3%), and an additional 25.1% of the main cohort consisted of untested patients (Table 1). When

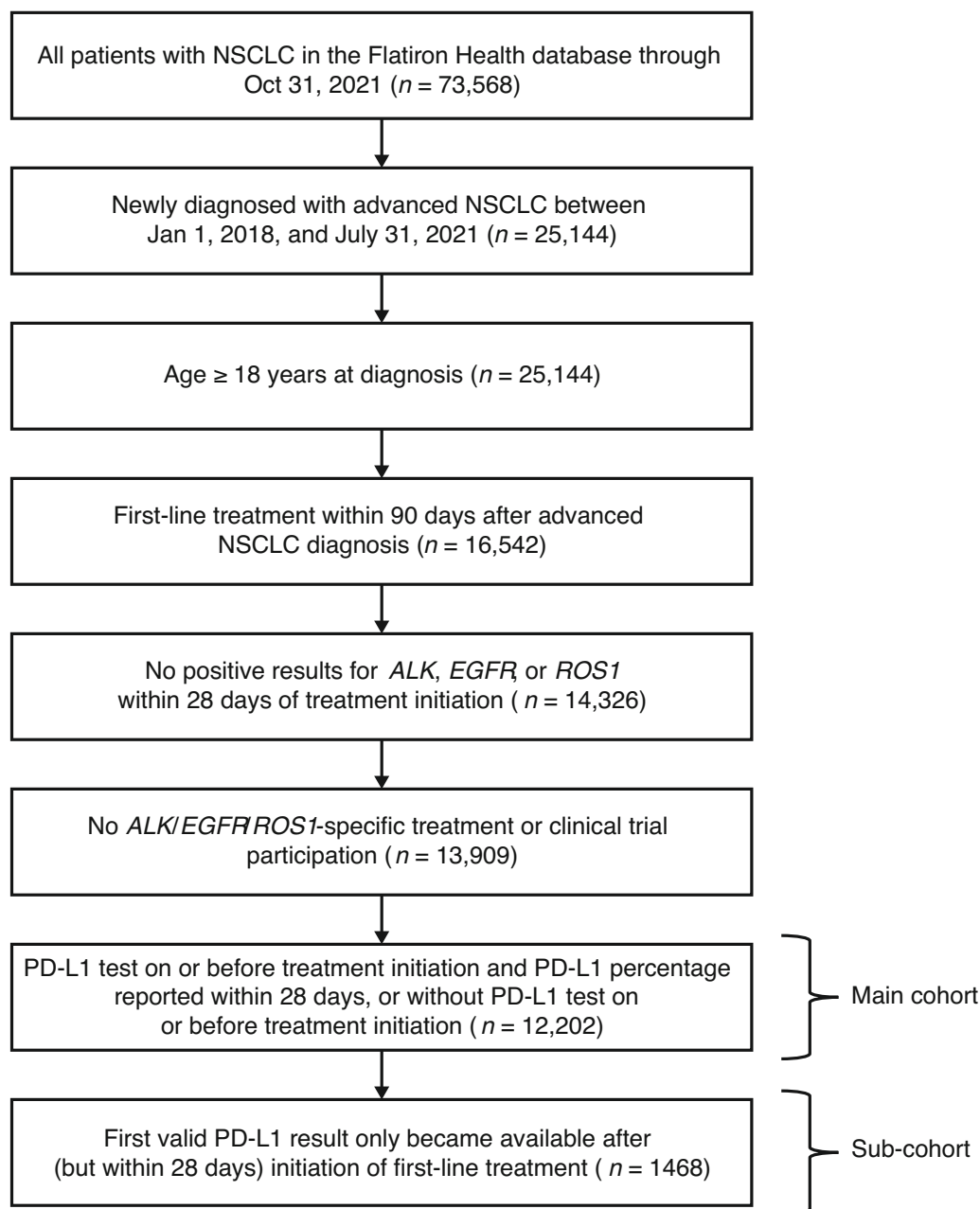


Fig. 1 Population attrition. *ALK* anaplastic lymphoma kinase, *EGFR* epidermal growth factor receptor, *NSCLC* non-small cell lung cancer, *PD-L1* programmed cell death-ligand 1, *ROS1* C-ROS oncogene 1

stratified by PD-L1 expression levels and testing status, most demographic and clinical characteristics were generally similar to the overall population (Table 1), except for a higher proportion of patients with squamous cell carcinoma among those who had no PD-L1 test

relative to those across the PD-L1 levels (39.5% vs. 24.9–30.6%, respectively).

Baseline characteristics of the sub-cohort were similar to those of the main cohort overall and across PD-L1 levels; 31.9%, 27.6%, and 40.5% of patients in the sub-cohort had PD-L1

Table 1 Demographic and clinical characteristics of the main cohort

| Variable | Total (<i>N</i> = 12,202) | PD-L1 results before, on, or within 28 days of first-line therapy initiation | | | No PD-L1 test (<i>n</i> = 3065) |
|---------------------------------|-------------------------------|--|-----------------------------------|----------------------------------|-------------------------------------|
| | | PD-L1 ≥ 50% (<i>n</i> = 3022) | PD-L1 1–49% (<i>n</i> = 2907) | PD-L1 < 1% (<i>n</i> = 3208) | |
| Age, years | | | | | |
| Mean (SD) | 69.2 (9.4) | 69.6 (9.7) | 69.2 (9.5) | 69.2 (9.3) | 68.9 (9.1) |
| Median (IQR) | 70 (63–77) | 70 (63–77) | 70 (63–77) | 70 (63–77) | 69 (63–76) |
| Age group, years, <i>n</i> (%) | | | | | |
| 18–44 | 117 (1.0) | 32 (1.1) | 35 (1.2) | 24 (0.8) | 26 (0.9) |
| 45–54 | 670 (5.5) | 170 (5.6) | 148 (5.1) | 184 (5.7) | 168 (5.5) |
| 55–64 | 2937 (24.1) | 706 (23.4) | 711 (24.5) | 766 (23.9) | 754 (24.6) |
| 65–74 | 4519 (37.0) | 1036 (34.3) | 1077 (37.1) | 1215 (37.9) | 1191 (38.9) |
| ≥ 75 | 3959 (32.5) | 1078 (35.7) | 936 (32.2) | 1019 (31.8) | 926 (30.2) |
| Sex, <i>n</i> (%) | | | | | |
| Female | 5532 (45.3) | 1468 (48.6) | 1331 (45.8) | 1374 (42.8) | 1359 (44.3) |
| Male | 6669 (54.7) | 1554 (51.4) | 1576 (54.2) | 1834 (57.2) | 1705 (55.6) |
| Unknown | 1 (< 0.1) | .— | .— | .— | 1 (< 0.1) |
| Race or ethnicity, <i>n</i> (%) | | | | | |
| Asian | 175 (1.4) | 43 (1.4) | 38 (1.3) | 48 (1.5) | 46 (1.5) |
| Black or African American | 1130 (9.3) | 253 (8.4) | 268 (9.2) | 312 (9.7) | 297 (9.7) |
| Other | 1331 (10.9) | 300 (9.9) | 341 (11.7) | 341 (10.6) | 349 (11.4) |
| White | 8118 (66.5) | 2034 (67.3) | 1921 (66.1) | 2152 (67.1) | 2011 (65.6) |
| Unknown | 1448 (11.9) | 392 (13.0) | 339 (11.7) | 355 (11.1) | 362 (11.8) |
| Geographic region, <i>n</i> (%) | | | | | |
| Midwest | 1779 (14.6) | 446 (14.8) | 424 (14.6) | 464 (14.5) | 445 (14.5) |
| Northeast | 2074 (17.0) | 553 (18.3) | 467 (16.1) | 551 (17.2) | 503 (16.4) |
| South | 5618 (46.0) | 1415 (46.8) | 1338 (46.0) | 1420 (44.3) | 1445 (47.2) |
| West | 1618 (13.3) | 402 (13.3) | 391 (13.5) | 419 (13.1) | 406 (13.3) |
| Unknown | 1113 (9.1) | 206 (6.8) | 287 (9.9) | 354 (11.0) | 266 (8.7) |
| Payer, <i>n</i> (%) | | | | | |
| Commercial | 6174 (50.6) | 1543 (51.1) | 1484 (51.1) | 1679 (52.3) | 1468 (47.9) |
| Medicare | 2465 (20.2) | 615 (20.4) | 584 (20.1) | 630 (19.6) | 636 (20.8) |
| Medicaid | 213 (1.8) | 43 (1.4) | 61 (2.1) | 59 (1.8) | 50 (1.6) |
| Other or unknown | 3350 (27.5) | 821 (27.2) | 778 (26.8) | 840 (26.2) | 911 (29.7) |

Table 1 continued

| Variable | Total (<i>N</i> = 12,202) | PD-L1 results before, on, or within 28 days of first-line therapy initiation | | | No PD-L1 test (<i>n</i> = 3065) |
|--|-------------------------------|--|-----------------------------------|----------------------------------|-------------------------------------|
| | | PD-L1 ≥ 50% (<i>n</i> = 3022) | PD-L1 1–49% (<i>n</i> = 2907) | PD-L1 < 1% (<i>n</i> = 3208) | |
| Histology, <i>n</i> (%) | | | | | |
| NSCLC histology NOS | 578 (4.7) | 163 (5.4) | 94 (3.2) | 135 (4.2) | 186 (6.1) |
| Non-squamous cell carcinoma | 7879 (64.6) | 2107 (69.7) | 1923 (66.2) | 2179 (67.9) | 1670 (54.5) |
| Squamous cell carcinoma | 3745 (30.7) | 752 (24.9) | 890 (30.6) | 894 (27.9) | 1209 (39.5) |
| ECOG performance status, <i>n</i> (%) | | | | | |
| 0 | 2845 (23.3) | 668 (22.1) | 642 (22.1) | 761 (23.7) | 774 (25.3) |
| 1 | 4386 (35.9) | 1101 (36.4) | 1048 (36.1) | 1167 (36.4) | 1070 (34.9) |
| 2 | 1737 (14.2) | 465 (15.4) | 452 (15.6) | 438 (13.7) | 382 (12.5) |
| 3 | 358 (2.9) | 113 (3.7) | 81 (2.8) | 81 (2.5) | 83 (2.7) |
| Missing or unknown | 2876 (23.6) | 675 (22.3) | 684 (23.5) | 761 (23.7) | 756 (24.7) |
| NSCLC occurrence, <i>n</i> (%) | | | | | |
| De novo | 9265 (75.9) | 2440 (80.7) | 2203 (75.8) | 2385 (74.4) | 2237 (73.0) |
| Recurrent | 2937 (24.1) | 582 (19.3) | 704 (24.2) | 823 (25.7) | 828 (27.0) |
| Sites of metastasis, ^a <i>n</i> (%) | | | | | |
| Liver or bile duct | 543 (4.5) | 141 (4.7) | 150 (5.2) | 158 (4.9) | 94 (3.1) |
| Brain or cerebral meninges | 1081 (8.9) | 323 (10.7) | 261 (9.0) | 329 (10.3) | 168 (5.5) |
| Bone or bone marrow | 2070 (17.0) | 564 (18.7) | 518 (17.8) | 605 (18.9) | 383 (12.5) |

ECOG Eastern Cooperative Oncology Group, *IQR* interquartile range, *NOS* not otherwise specified, *NSCLC* non-small cell lung cancer, *PD-L1* programmed cell death-ligand 1, *SD* standard deviation

^aFor individual sites of metastasis, only those present in ≥ 5% of patients with any PD-L1 expression level before first-line therapy are shown

expression ≥ 50%, 1–49%, and < 1%, respectively (Table S1).

First-Line Treatment Landscape

As shown in Fig. 2, there were changes in the first-line treatment landscape from 2018 to 2019 followed by relative stability in type of first-line treatment initiated in each of the PD-

L1 strata among patients with PD-L1 test results. ICIs were the predominant treatment (> 60% of patients from 2019 onward) as either monotherapy or ICI + chemotherapy. In the PD-L1 < 1% group, there was a notable reduction in chemotherapy alone between 2018 (49.0%) and 2019 (30.1%) and a corresponding increase in ICI-based treatment from 46.6% to 65.7% (Fig. 2a). In the PD-L1 1–49% group (Fig. 2b), there was a smaller but noticeable shift

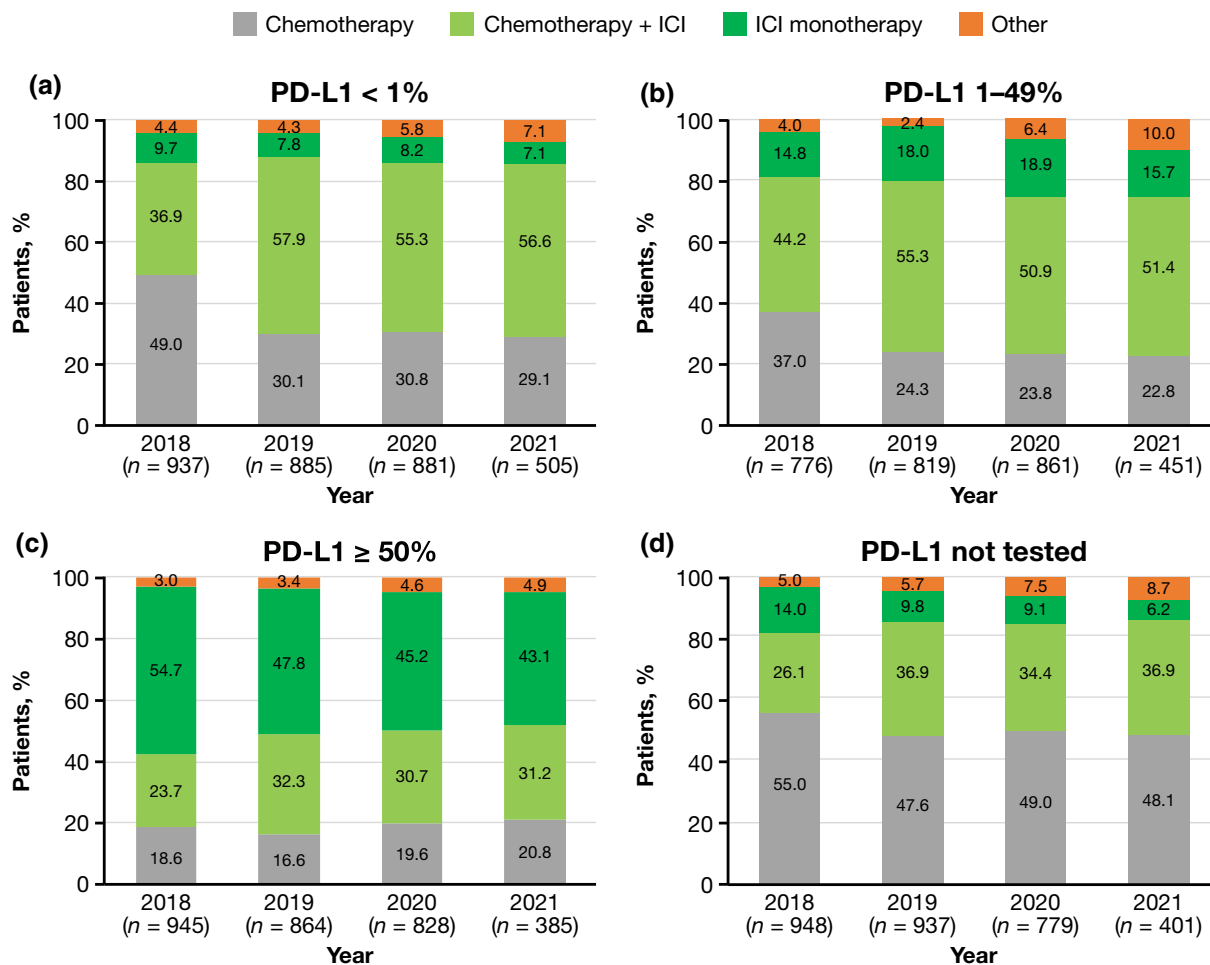


Fig. 2 Distribution of first-line treatment stratified by PD-L1 expression and year among patients with newly diagnosed advanced non-small cell lung cancer. *ICI* immune checkpoint inhibitor, *PD-L1* programmed cell death-ligand 1

from chemotherapy alone (37.0%–24.3%) to ICI-based treatment regimens (59.0%–73.3%) from 2018 to 2019. Between 2019 and 2021, chemotherapy use appeared to stabilize across PD-L1 expression levels and accounted for 20.8–29.1% of first-line treatment in 2021 (Fig. 2a–c). Use of ICI + chemotherapy was most common among patients with PD-L1 < 1% and PD-L1 1–49% (Fig. 2a and b), whereas ICI monotherapy was most common (43.1–54.7%) among patients with PD-L1 ≥ 50% (Fig. 2c).

Among patients not tested for PD-L1, there were few changes in treatment patterns. Chemotherapy alone remained the most common first-line treatment between 2018 and 2021 (47.6–55.0%), followed by ICI + chemotherapy

(26.1–36.9%) and ICI monotherapy (6.2–14.0%) (Fig. 2d).

Treatment Patterns Among Patients Initiating First-Line Treatment Before PD-L1 Test Results

In the sub-cohort, ICI + chemotherapy was the most common treatment before obtaining the PD-L1 test results and was received by 42.6% of patients (Table 2). ICI monotherapy was the least common treatment, received by 5.6% of patients, with chemotherapy alone and other therapies received by 35.6% and 15.7% of patients, respectively. Baseline characteristics were generally similar between patients

Table 2 Demographic and clinical characteristics of the sub-cohort of patients who received therapy before PD-L1 test results stratified by the type of therapy received before these results ($n = 1468$)

| Variable | Chemotherapy ($n = 523$) | ICI monotherapy ($n = 82$) | ICI + chemotherapy ($n = 626$) | Other ($n = 237$) |
|----------------------------|-------------------------------|---------------------------------|-------------------------------------|------------------------|
| Age, years | | | | |
| Mean (SD) | 68.2 (9.5) | 73.0 (9.5) | 68.8 (8.9) | 69.0 (9.8) |
| Median (IQR) | 69 (62–75) | 74.5 (67–81) | 70 (62–75) | 70 (63–76) |
| Age group, years, n (%) | | | | |
| 18–44 | 5 (1.1) | ≤ 5 | 5 (0.8) | 5 (2.1) |
| 45–54 | 27 (6.0) | ≤ 5 | 31 (5.0) | 16 (6.8) |
| 55–64 | 125 (27.7) | 12 (14.6) | 158 (25.2) | 50 (21.1) |
| 65–74 | 161 (35.6) | 26 (31.7) | 256 (40.9) | 87 (36.7) |
| ≥ 75 | 134 (29.7) | 41 (50.0) | 176 (28.1) | 79 (33.3) |
| Sex, n (%) | | | | |
| Female | 182 (40.3) | 28 (34.2) | 262 (41.9) | 114 (48.1) |
| Male | 270 (59.7) | 54 (65.9) | 364 (58.2) | 124 (51.9) |
| Race or ethnicity, n (%) | | | | |
| Asian | 7 (1.3) | ≤ 5 | 8 (1.3) | 4 (1.7) |
| Black or African American | 32 (6.1) | ≤ 5 | 44 (7.0) | 23 (9.7) |
| Other | 63 (12.1) | ≤ 5 | 86 (13.7) | 19 (8.0) |
| White | 351 (67.1) | 65 (79.3) | 401 (64.1) | 171 (75.2) |
| Unknown | 70 (13.4) | 7 (8.5) | 87 (13.9) | 20 (8.4) |
| Geographic region, n (%) | | | | |
| Midwest | 79 (15.1) | 8 (9.8) | 76 (12.1) | 33 (13.9) |
| Northeast | 114 (21.8) | 17 (20.7) | 124 (19.8) | 62 (26.2) |
| South | 220 (42.1) | 37 (45.1) | 291 (46.5) | 98 (41.4) |
| West | 90 (17.1) | 17 (20.7) | 106 (16.9) | 21 (8.9) |
| Unknown | 20 (3.8) | 3 (3.7) | 29 (4.6) | 23 (9.7) |
| Payer, n (%) | | | | |
| Commercial | 286 (54.7) | 44 (53.7) | 346 (55.3) | 111 (46.8) |
| Medicare | 84 (16.1) | 17 (20.7) | 134 (21.4) | 46 (19.4) |
| Medicaid | 9 (1.7) | — | 8 (1.3) | 6 (2.5) |
| Other or unknown | 144 (27.5) | 21 (25.6) | 138 (22.0) | 74 (31.2) |

Table 2 continued

| Variable | Chemotherapy (<i>n</i> = 523) | ICI monotherapy (<i>n</i> = 82) | ICI + chemotherapy (<i>n</i> = 626) | Other (<i>n</i> = 237) |
|--|-----------------------------------|-------------------------------------|---|----------------------------|
| Histology, <i>n</i> (%) | | | | |
| NSCLC histology NOS | 31 (5.9) | 5 (6.1) | 43 (6.9) | 13 (5.5) |
| Non-squamous cell carcinoma | 316 (60.4) | 47 (57.3) | 452 (72.2) | 157 (66.2) |
| Squamous cell carcinoma | 176 (33.7) | 30 (36.6) | 131 (20.9) | 67 (28.3) |
| ECOG performance status, <i>n</i> (%) | | | | |
| 0 | 127 (24.3) | 15 (18.3) | 147(23.5) | 57 (24.1) |
| 1 | 183 (35.0) | 27 (32.9) | 227 (36.3) | 79 (33.3) |
| 2 | 66 (12.6) | 17 (20.7) | 53 (8.5) | 34 (14.4) |
| 3 | 12 (2.3) | 3 (3.7) | 13 (2.1) | 10 (4.2) |
| Missing or unknown | 135 (25.8) | 20 (24.4) | 186 (29.7) | 57 (24.1) |
| NSCLC occurrence, <i>n</i> (%) | | | | |
| De novo | 449 (85.9) | 49 (56.8) | 567 (90.6) | 213 (89.9) |
| Recurrent | 74 (14.2) | 33 (40.2) | 59 (9.4) | 24 (10.1) |
| Sites of metastasis, ^a <i>n</i> (%) | | | | |
| Lung | 9 (1.7) | 5 (6.1) | 26 (4.2) | 5 (2.1) |
| Liver or bile duct | 21 (4.0) | 7 (8.5) | 37 (5.9) | 14 (5.9) |
| Brain or cerebral meninges | 25 (4.8) | 6 (7.3) | 39 (6.2) | 18 (7.6) |
| Bone or bone marrow | 74 (14.1) | 10 (12.2) | 155 (24.8) | 54 (22.8) |

ECOG Eastern Cooperative Oncology Group, IQR interquartile range, NOS not otherwise specified, NSCLC non-small cell lung cancer, PD-L1 programmed cell death-ligand 1, SD standard deviation

^aFor individual sites of metastasis, only those present in $\geq 5\%$ of patients with any PD-L1 expression level prior to first-line therapy are shown

initiating chemotherapy alone and ICI + chemotherapy, except for a lower percentage of patients with squamous cell carcinoma histology in those who received ICI + chemotherapy (20.9%) relative to chemotherapy alone (33.7%). Relative to the other treatment categories, patients who received ICI monotherapy were slightly older (mean age 73.0 years vs. 68.2–69.0 years) and more likely to have recurrent disease (40.2% vs. 9.4–14.2%) (Table 2).

At 45 days after receiving PD-L1 test results, most patients at each PD-L1 level remained on

the same treatment as before the PD-L1 test results regardless of treatment type, except for those who had received other therapies (Fig. 3); 50.1–62.0% of patients who received other therapies before the test results received ICIs, as either monotherapy or ICI + chemotherapy, after receiving test results. Of the patients who received chemotherapy alone before test results, 21.1–35.3% received ICIs as either monotherapy or ICI + chemotherapy after the test results, with the highest proportion of any ICI use among those with PD-L1 $\geq 50\%$. Across PD-L1 levels, 28.0–30.0% of patients who received

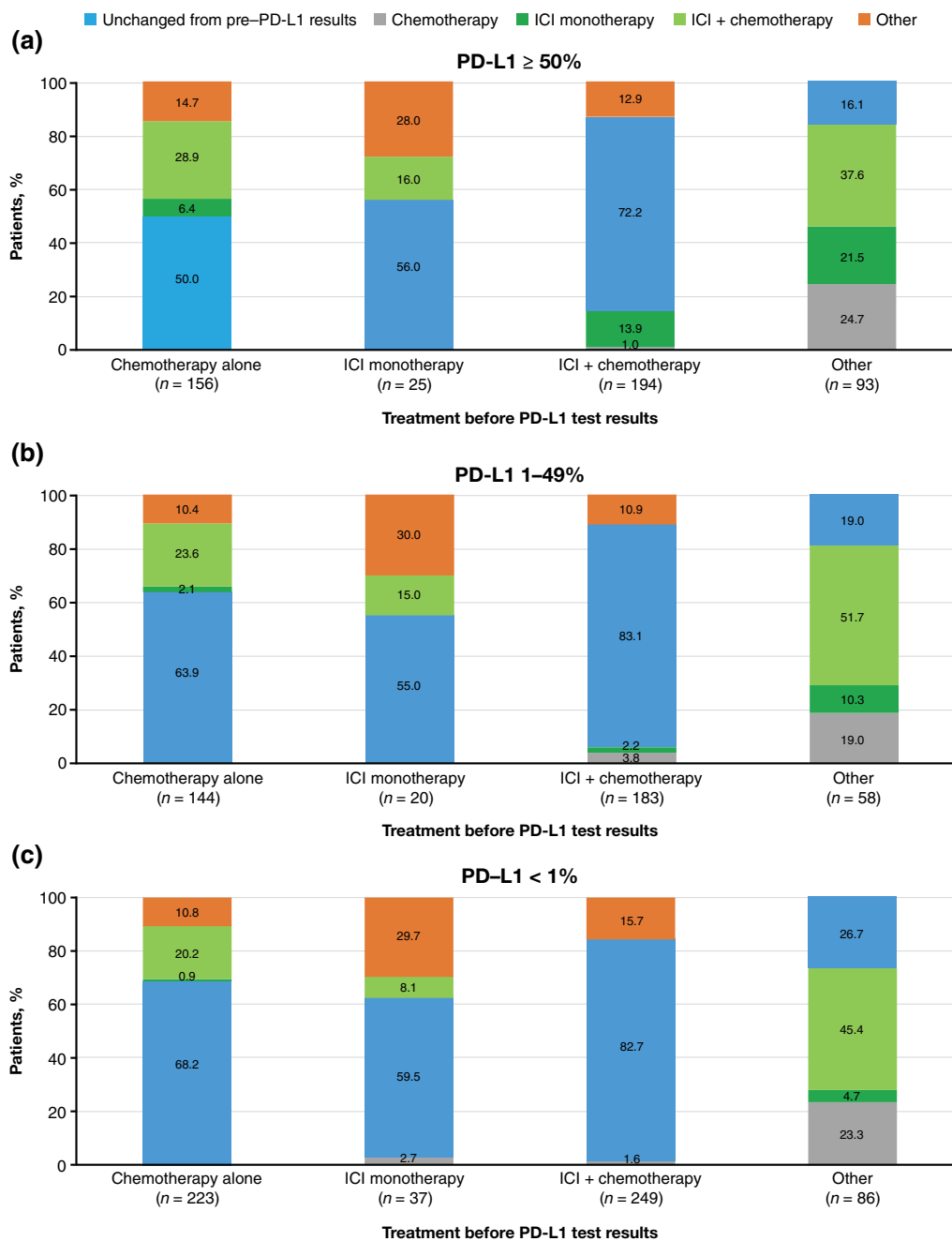


Fig. 3 Distribution of treatment after receiving PD-L1 test results by type of treatment received before PD-L1 test results. *ICI* immune checkpoint inhibitor, *PD-L1* programmed cell death-ligand 1

ICI monotherapy before the PD-L1 test results received other therapies or no therapy after receiving the test results.

Probability of Receiving ICIs After PD-L1 Test Results Among First-Line Chemotherapy-Treated Patients

Among the sub-cohort of patients who were receiving chemotherapy alone (*n* = 523) before

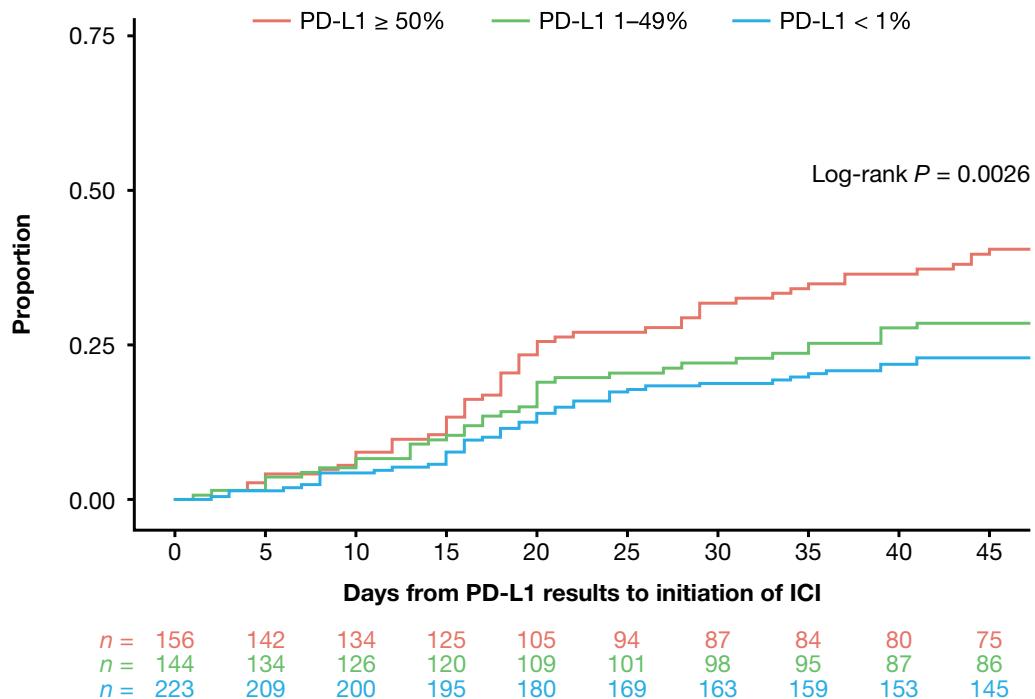


Fig. 4 Probability of receiving ICI therapy within 45 days after receiving PD-L1 test results among patients with newly diagnosed advanced non-small cell lung cancer who

initiated chemotherapy as first-line treatment before PD-L1 test results. *ICI* immune checkpoint inhibitor, *PD-L1* programmed cell death-ligand 1

PD-L1 test results, the probability of receiving ICIs over the 45-day period after PD-L1 test results was highest among patients with PD-L1 \geq 50% (log-rank $p = 0.0026$) (Fig. 4). The probability of switching to or adding an ICI was 40.5% (95% CI 31.6–48.3%), 28.6% (95% CI 20.3–36.0%), and 22.9% (95% CI 16.9–28.4%) for patients with PD-L1 \geq 50%, 1–49%, and < 1%, respectively.

The association of sociodemographic and clinical characteristics with receipt of ICIs after receipt of PD-L1 test results among the patients who were previously receiving chemotherapy alone are reported in Table 3. During the 45 days after receiving PD-L1 results, patients with PD-L1 \geq 50%, bone or bone marrow metastasis, higher ECOG performance status, or receiving treatment in later years were more likely to receive ICIs. PD-L1 \geq 50% increased the likelihood of receiving ICIs by 93% relative to PD-L1 < 1% (HR 1.93; 95% CI 1.27–2.93). The strongest association was for bone or bone

marrow metastasis, with a 2.5-fold higher likelihood of receiving ICIs (HR 2.59; 95% CI 1.63–3.84) relative to no metastasis at this site, followed by receiving treatment in the years 2020 and 2021, both with a slightly more than twofold likelihood compared with 2018 [HRs of 2.32 (95% CI 1.45–3.71) and 2.02 (95% CI 1.23–3.31), respectively]. Patients with an ECOG performance status of 2–4 were 56% more likely to receive ICIs than those with ECOG performance status 0 or 1 (HR 1.56; 95% CI 0.96–2.53). Patients with squamous cell carcinoma histology were 53% less likely to receive ICIs (HR 0.47; 95% CI 0.30–0.72).

DISCUSSION

In this large real-world cohort of patients with aNSCLC who had no known *ALK*, *EGFR*, or *ROS1* aberrations and who initiated first-line treatment, we observed increased uptake of ICIs

Table 3 Cox proportional hazards model estimates for receiving immune checkpoint inhibitors by 45 days after receiving PD-L1 test results among patients who received chemotherapy alone before PD-L1 test results

| Variable (reference) | HR (95% CI) |
|---|-------------------|
| PD-L1 level (< 1%) | |
| ≥ 50% | 1.93 (1.27, 2.93) |
| 1–49% | 1.19 (0.76, 1.86) |
| Age group, years (18–54) | |
| 55–64 | 1.48 (0.67, 3.29) |
| 65–74 | 1.70 (0.78, 3.74) |
| ≥ 75 | 1.42 (0.63, 3.21) |
| Male (female) | 1.35 (0.94, 1.94) |
| Geographic region (South) | |
| Midwest | 1.04 (0.63, 1.72) |
| Northeast | 0.97 (0.61, 1.54) |
| West | 1.22 (0.74, 2.02) |
| Race or ethnicity (White) | |
| Black | 0.87 (0.39, 1.94) |
| Other or unknown | 0.96 (0.64, 1.44) |
| Payer (commercial) | |
| Medicare | 0.81 (0.47, 1.38) |
| Medicaid | 0.41 (0.06, 3.04) |
| Other or unknown | 1.38 (0.94, 2.03) |
| Histology (non-squamous cell carcinoma) | |
| NSCLC histology NOS | 0.62 (0.26, 1.45) |
| Squamous cell carcinoma | 0.47 (0.30, 0.72) |
| ECOG performance status (0 or 1) | |
| 2–4 | 1.56 (0.96, 2.53) |
| Missing | 1.09 (0.71, 1.67) |
| Site of metastasis (no metastasis at the specific site) | |
| Liver or bile duct | 1.51 (0.61, 3.73) |
| Brain or cerebral meninges | 1.95 (1.01, 3.78) |
| Bone or bone marrow | 2.50 (1.63, 3.84) |
| Any other primary cancer (none) | 0.98 (0.53, 1.82) |
| Smoker (nonsmoker) | 0.63 (0.33, 1.18) |

Table 3 continued

| Variable (reference) | HR (95% CI) |
|--------------------------------|-------------------|
| Recurrent occurrence (de novo) | 0.87 (0.51, 1.48) |
| Index year (2018) | |
| 2019 | 1.63 (1.00, 2.67) |
| 2020 | 2.32 (1.45, 3.71) |
| 2021 | 2.02 (1.23, 3.31) |

CI, confidence interval, ECOG Eastern Cooperative Oncology Group, HR hazard ratio, NOS not otherwise specified, NSCLC non-small cell lung cancer, PD-L1 programmed cell death-ligand 1

between 2018 and 2019 across PD-L1 levels. By 2021, approximately 20–30% of PD-L1-tested patients received chemotherapy alone as first-line treatment. In approximately 25% of patients, first-line treatment was initiated before PD-L1 testing, of whom nearly half received chemotherapy alone as first-line treatment during each study year. Among patients who initiated chemotherapy alone before receiving their PD-L1 test result, more than half remained on chemotherapy after receiving PD-L1 results, and only 21.1–35.3% subsequently received ICIs even in high PD-L1 expressers.

Published studies evaluating treatment patterns for aNSCLC describe a shift in treatment modalities that supports rapid acceptance and clinical uptake of ICIs immediately following their approval and incorporation into guidelines [13–17]. The current study showed that these shifts to ICIs have been maintained. The small to moderate increases in ICI use between 2018 and 2019 for patients with low and negative PD-L1, in contrast to the consistently higher use of ICIs among patients with PD-L1 ≥ 50% during these 2 years, likely reflects recognition of the expanded indication for these drugs and release of data on ICI combination therapy [20, 21]. Patterns of first-line treatment for patients with aNSCLC in real-world clinical settings subsequently remained stable across all PD-L1 levels through the end of the study period (October 31, 2021). Regardless

of PD-L1 expression, ICIs as monotherapy or in combination with chemotherapy were the predominant first-line treatment and were initiated in 59.0–80.0% of patients. The most frequent use of ICIs was among patients with high levels of PD-L1 expression, who were also the most likely to receive ICIs as monotherapy.

These results are consistent with and expand on a previous study of treatment patterns through 2018 also using the Flatiron Health aNSCLC database [13]. Also consistent with that study, our results suggest that even if first-line treatment utilization in most patients was concordant with current recommendations, a substantial proportion of patients continued to initiate either chemotherapy alone or other non-ICI treatments as first-line therapy. While the reason for these treatment decisions could not be determined in our study, clinicians and patients may consider specific factors other than treatment guidelines when deciding not to use ICIs. In particular, 24.1% of patients with aNSCLC had recurrent disease rather than a de novo diagnosis, and it is possible that patients with recurrent disease who progressed to advanced-stage disease were less likely to use ICI as first-line therapy if they had previously received these drugs. In our study, patients with recurrent (vs. de novo) aNSCLC who received chemotherapy alone before PD-L1 test results had a lower, albeit nonsignificant, likelihood of receiving ICI after receiving PD-L1 test results. Another potential reason for not using ICIs may be contraindications such as the presence of genomic aberrations; however, this study excluded patients with *ALK*, *EGFR*, and *ROS1* aberrations or who received targeted treatments for such aberrations. While autoimmune disease or immunosuppressive treatments may also impact treatment choices, other real-world studies have shown that ICI use is not uncommon in these patients [22–24]. Finally, socioeconomic barriers may also impact choice of therapy, and additional studies are needed to further explore the factors influencing treatment decisions.

In contrast to patients with known PD-L1 levels, chemotherapy alone was the most frequent first-line therapy (47.6–55.0%) among patients not tested for PD-L1 expression across

all years. While there appeared to be a small shift to greater use of ICI + chemotherapy between 2018 and 2019, with a concomitant decline in chemotherapy alone, the treatment paradigm appeared to remain stable in subsequent years. Approximately 20% of patients did not undergo testing for PD-L1, which was slightly less than the 29.6% previously reported for an earlier time period [14]. Reasons for not testing have not been well studied and may include frailty, comorbidities, and overall benefit–risk assessment. Adhering to recommendations for PD-L1 testing, when appropriate, with timely testing and accurate reporting could help inform and optimize first-line treatment choices for aNSCLC.

The reasons for not initiating ICIs after receiving positive PD-L1 results were unknown, but may be due to a lack of awareness by providers, difficulty accessing appropriate testing or medication, or financial factors. Among patients who initiated chemotherapy alone before PD-L1 results, approximately half remained on chemotherapy regardless of PD-L1 testing results. Chemotherapy is associated with well-recognized adverse events that are reported by patients to negatively impact function and quality of life in a manner that may offset potential treatment benefits [25–27]. Additionally, clinical studies have demonstrated that ICIs convey clinically meaningful overall survival benefits with lower rates of specific toxicities, and improve patient-reported outcomes versus chemotherapy [5–8].

Patients with high PD-L1 expression levels, which accounted for approximately one third of all patients tested for PD-L1, were more likely to receive ICIs after receiving test results. This observation was not surprising, given that the initially approved indication for first-line use was for patients expressing high levels of PD-L1. However, even among patients who subsequently received a PD-L1 $\geq 50\%$ test result after initiating chemotherapy, only 40% received ICI within the subsequent 45 days. The strongest association appeared to be for the presence of bone or bone marrow metastasis, with an almost 2.5-fold higher likelihood of receiving ICI therapy at 45 days. Despite poorer prognosis reported among patients with aNSCLC and

bone metastasis, partial or complete response to ICIs has been reported [28–30]. Having squamous cell carcinoma histology was associated with a significantly lower likelihood of ICI, which could be partially due to the later approval of ICI + chemotherapy in this group relative to those with non-squamous cell carcinoma.

Limitations

Several study limitations should be considered, including that EHRs do not capture the full range of clinical variables (e.g., physician or patient preference), and data on some variables that may contribute to treatment decisions were incomplete or unavailable (e.g., ECOG performance status). Additional research is warranted to understand the determinants of treatment choices, especially the use of chemotherapy alone in the first line among patients with aNSCLC without *ALK*, *EGFR*, or *ROS1* genomic aberrations. Studies are also needed to evaluate the impact on treatment outcomes of enhanced treatment decision-making based on timely biomarker testing. As information on LOTs are not routinely recorded in the EHR, LOT characterization is driven by Flatiron Health's proprietary oncologist-defined algorithms and may not accurately reflect the actual LOTs. Another limitation is that the sample size for the sub-cohort was relatively small. Finally, the Flatiron Health database predominantly reflects community oncology centers, with only a small proportion of patients attending academic medical centers, limiting the generalizability of the results to the broader population of patients with aNSCLC.

CONCLUSIONS

This real-world study showed that ICI use accounted for most first-line aNSCLC treatment, concordant with guideline recommendations; however, a substantial proportion of patients across PD-L1 expression levels were initiated on non-ICI therapies, especially chemotherapy alone. Up to 2021, one out of five patients did not get tested for PD-L1, of

whom almost half initiated chemotherapy alone as first-line treatment. Furthermore, a substantial portion of patients who initiated therapy before PD-L1 test results were found to receive chemotherapy alone and most of these remained on this regimen despite subsequently receiving positive PD-L1 results. Overall, these results highlight the fact that despite meaningful uptake in PD-L1 testing and use of ICIs as first-line therapy for aNSCLC, many patients do not receive guideline-directed biomarker testing or guideline-directed therapy based on their biomarker status; adherence to guidelines for biomarker testing may help optimize personalized treatment for aNSCLC.

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Compliance with Ethics Guidelines. Institutional Review Board (WCG IRB, Puyallup, WA) approval of the study protocol was obtained before study conduct and included a waiver of informed consent.

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 de-identified 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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