# Real-World Clinical Impact of Immune Checkpoint Inhibitors in Patients With Advanced/Metastatic Non–Small Cell Lung Cancer After Platinum Chemotherapy

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## Abstract

**We compared real-world data from US patients who received second-line (2L) therapy for non–small-cell lung cancer before ("historical") and after ("current") US Food and Drug Administration approval of programmed death ligand 1 (PD-L1) inhibitors. A greater proportion of patients received 2L therapy in the current compared with the historical setting; approximately half of current patients received 2L PD-L1 inhibitors. Survival was improved by 15% in the current setting.**

**Background:** The real-world effect of anti-programmed death ligand 1 (PD-L1) therapies is unclear. We compared US patients who received second-line therapy for non–small-cell lung cancer (NSCLC) before and shortly after US Food and Drug Administration (FDA) approval of PD-L1 inhibitors. **Patients and Methods:** Patients in the Flatiron Health database (≥18 years; received first-line platinum therapy for advanced/metastatic NSCLC; ≥6 months of follow-up) were assessed before ("historical": January 1, 2011 to December 31, 2013) and after ("current": January 1, 2015 to May 31, 2017) FDA approval of anti–PD-L1 therapies for NSCLC. Index was start of second-line therapy. Baseline variables, treatment patterns, and overall survival (OS) were reported. **Results:** A greater proportion of patients in the current cohort received second-line treatment than in the historical cohort (n = 4240 [57.0%] vs. n = 2357 [37.4%]); 48.8% [n = 2071] of the current second-line patients received anti–PD-L1 therapy. Current patients were more likely to receive second-line anti–PD-L1 therapy if they had poorer Eastern Cooperative Oncology Group (ECOG) performance status (≥2), had squamous histology, or had no epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), or ROS proto-oncogene 1 mutations. Median OS from index was higher in the current cohort (9.4 [95% confidence interval (CI), 8.9-9.9] months) than the historical cohort (7.3 [95% CI, 6.9-7.8] months). Adjusted for sex, race, ECOG performance status, disease stage, and Kirsten rat sarcoma viral oncogene homolog, *EGFR*, and *ALK* status, OS was improved by 15% in the current cohort. **Conclusion:** Contemporary patients are more likely to receive second-line therapy and have longer OS than patients who received care before approval of anti–PD-L1 therapies.

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**Keywords:** Immunotherapy, NSCLC, Observational, Second-line, Utilization patterns

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## Introduction

Lung cancer is the second most common malignancy in men and women, and the leading cause of cancer-related mortality in the United States, which was projected to account for approximately 154,000 deaths annually in 2018.[1] Approximately 85% of lung cancers are non–small-cell lung cancer (NSCLC), which, in the United States, is comprised of nonsquamous (70%), squamous (25%), and nonspecified (5%) histologies.[2,3] More than half of all


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lung cancers in the United States are diagnosed at advanced or metastatic stage,[2,4] which has a 5-year survival of 4.8%.[5]

The recommendations for systemic treatment of metastatic NSCLC (stage IV) are guided by patient performance status (PS), tumor histology, and status of tumor biomarkers. Patients whose tumors harbor sensitizing mutations in epidermal growth factor receptor (*EGFR*), B-Raf proto-oncogene, anaplastic lymphoma kinase (*ALK*) gene rearrangement, or proto-oncogene receptor tyrosine kinase ROS proto-oncogene 1 (*ROS1*) gene fusion are treated with tyrosine kinase inhibitors. For all other patients, first-line (1L) treatment with platinum-based chemotherapy has long been the standard of care, although recent approvals of immune checkpoint inhibitors targeting the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) pathway have changed the clinical landscape.[6]

In the second-line (2L) setting after 1L chemotherapy, the efficacy and safety of anti−PD-L1 therapies have been shown in several phase III clinical trials. In March 2015, nivolumab was granted approval by the US Food and Drug Administration (FDA) for treatment of metastatic squamous NSCLC after progression with previous platinum-based therapy,[7] and this indication was expanded in October 2015 to include nonsquamous NSCLC.[8] The approval was on the basis of the results of the phase III CheckMate 017[9] and CheckMate 057 trials,[10] which showed an overall survival (OS) advantage of nivolumab compared with docetaxel in patients with squamous and nonsquamous metastatic NSCLC, respectively. Also in October 2015, a second PD-1 inhibitor, pembrolizumab, was granted accelerated FDA approval for treatment of PD-L1−positive NSCLC after previous platinum-based therapy,[11] on the basis of favorable efficacy compared with docetaxel, as noted in the phase II/III KEYNOTE-010 trial.[12] In October 2016, the FDA approved the PD-L1 inhibitor atezolizumab for treatment of metastatic NSCLC after progression with previous platinum-based therapy,[13] largely on the basis of improved outcomes in patients who received atezolizumab in the phase III OAK trial compared with those who received docetaxel.[14]

Few publications report real-world data identifying treatment patterns and clinical outcomes of patients who previously received platinum-based systemic therapy for advanced/metastatic NSCLC,[3,15-18] and none have compared OS before and after the availability of anti−PD-L1 therapies for NSCLC after platinum-based therapy in US clinical practice. This study aimed to address this knowledge gap by assessing real-world treatment patterns and clinical outcomes of US patients with advanced/metastatic NSCLC who received 2L treatment after platinum-based therapy, comparing time periods before and after the FDA approval of PD-L1 inhibitors.

## Patients and Methods

### *Data Source*

This retrospective, observational study used deidentified, patient-level data from the Flatiron Health electronic health record database, a demographically and geographically diverse repository representing > 2 million patients with cancer, with data submitted by approximately 2500 clinicians at more than 265 oncology clinics throughout the United States.[19] The Flatiron Health database has been shown to be nationally representative of the US oncology setting.[20]

### *Patients and Study Design*

Patients were included if they were 18 years of age or older at diagnosis and diagnosed with advanced/metastatic NSCLC (stage IIIB/IV), or with early-stage NSCLC and subsequent progression to advanced/metastatic disease, between January 1, 2011 and May 31, 2017. Data were collected until November 30, 2017, to ensure sufficient maturity; a relatively long study period was needed to permit 6 months of follow-up for all patients. Patients had at least 1 systemic treatment after diagnosis of advanced/metastatic disease, and started treatment of advanced/metastatic NSCLC with 1L platinum-based therapy. The first observed date of initiation of 2L therapy was considered the index date. Patients were followed until the date of the last observed visit or medication administration, death, or end of the study period. Patients who had participated in any clinical trial, had evidence of any other primary cancer diagnosis during the study period, or had received targeted therapy or immunotherapy before the date of advanced/metastatic diagnosis were excluded.

Two cohorts were identified, representing periods before and after FDA approval of anti−PD-L1 therapies: "historical" (patients with a diagnosis of advanced/metastatic NSCLC who received 2L treatment between January 1, 2011 and December 31, 2013) and "current" (patients with a diagnosis of advanced/metastatic NSCLC who received 2L treatment between January 1, 2015 and May 31, 2017). Patients who received 2L treatment between January 1, 2014 and December 31, 2014 were excluded (this was considered a "washout period") to minimize any potential crossover effect between cohorts (ie, patients in the historical cohort who received anti−PD-L1 therapy after FDA approval) and to enable assessment of the effect of immuno-oncology treatment after initiation of ≥2L therapy.

### *Study Outcomes*

Baseline variables were assessed and compared between patients in the current and historical cohorts. We also compared baseline variables in patients who did and did not receive anti−PD-L1 therapy in the 2L by assessing 2 subgroups of the current cohort: patients who received anti−PD-L1 therapies in the 2L ("current 2L anti−PD-L1") and patients with no record of having received anti−PD-L1 therapies in the 2L ("current 2L non-anti−PD-L1"). The first observed record of platinum-based therapy after diagnosis of advanced/metastatic NSCLC was considered 1L. Switching to another platinum-based therapy with a treatment gap of <42 days was considered the same line of therapy, as defined previously.[21] A line of therapy advanced with each new treatment recorded in the database and was considered a combination regimen if 2 or more different medications were administered within 30 days of each other, with a repeat administration of the initial medication recorded within 60 days. Duration of therapy was defined as the period between the first and last record of administration for that line of therapy. OS was calculated from the index date until the date of death, last known follow-up, or end of study period. Landmark survival was calculated as the percentage of patients surviving at 6, 12, and 24 months after the index date.

### *Statistical Analysis*

Baseline demographic and patient characteristics are reported descriptively. Frequencies and proportions are used to describe

categorical data, and mean (SD) and median (range) are used to describe continuous data. $\chi^2$ tests were used to assess the distribution of categorical variables between cohorts (and Fisher exact test if more than half the values relating to a variable were <5); on the basis of data distribution, Wilcoxon rank sum test was used to assess continuous variables. Kaplan–Meier product limit estimates were used for the unadjusted analyses of OS and duration of therapy by cohort. Because the characteristics of patients who received 2L treatment might change over time, Cox proportional hazards models of OS were used to estimate hazard ratios (HRs) across current and historical 2L cohorts, in unadjusted and adjusted models accounting for patient demographic and clinical variables. Logistic regression was used to assess the association of multiple demographic and clinical parameters with the likelihood of receiving 2L anti–PD-L1 therapies. Statistical analyses were conducted using SAS 9.4 software (SAS Institute Inc, Cary, NC).

## Results

In total, 6306 patients in the historical cohort (January 1, 2011 to December 31, 2013) and 7438 patients in the current cohort (January 1, 2015 to May 31, 2017) diagnosed with advanced NSCLC who had received 1L platinum-based therapy with at least 6 months of follow-up were identified in the Flatiron Health database. Of these, 2357 patients (37.4%) in the historical cohort received 2L treatment, and 1123 patients (17.8%) received third-line (3L) treatment (Figure 1). In the current cohort, 4240 patients (57.0%) received 2L treatment, and 1875 patients (25.2%) received 3L treatment.

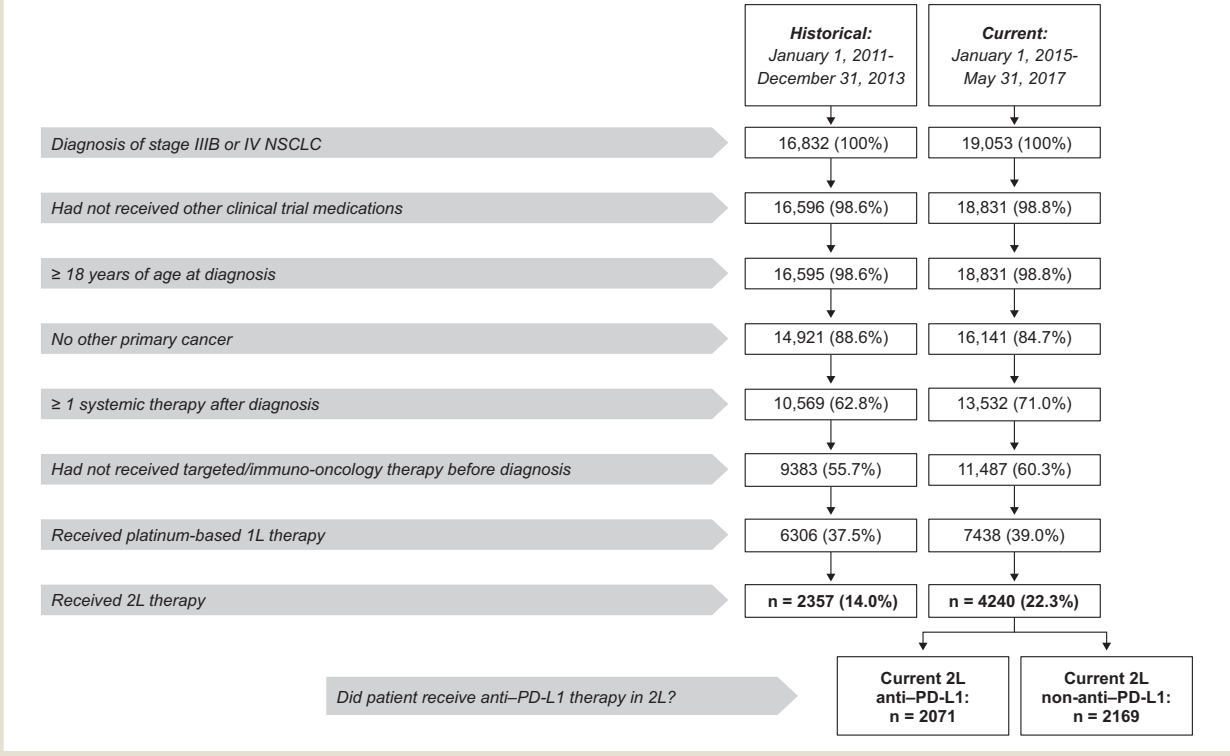
### *Historical Versus Current Cohorts: Baseline Characteristics*

Patients in the historical and current cohorts were similar in terms of distribution of sex and race (Table 1). There were no differences in age, sex, race, and disease stage at diagnosis in patients with and without available Eastern Cooperative Oncology Group (ECOG) PS data (data not shown). A comparison of the oncogenic testing patterns of patients in the historic and current cohorts is presented in Supplemental Table 1 in the online version. Median duration of follow-up from index (2L initiation) until the date of the last observed visit or medication administration, death, or end of the study period was 5.4 (range, 0.03-76.9) months in the historical cohort and 6.3 (range, 0.03-34.8) months in the current cohort. Notably, a smaller proportion of patients received a 2L treatment after platinum-based therapy in the historical cohort compared with the current cohort (37.4% vs. 57.0%; Table 2).

### *Clinical Characteristics Associated With the Real-World Uptake of Anti–PD-L1 Therapy*

Among patients in the current cohort who received 2L therapy (n = 4240), approximately half (n = 2071; 48.8%) received anti–PD-L1 therapy, with the other half receiving non-anti–PD-L1 therapies (n = 2169; 51.2%; Table 2). Uptake of anti–PD-L1

**Figure 1** Attrition of Historical and Current Patient Cohorts




Abbreviations: 1L = first-line; 2L = second-line; NSCLC = non–small-cell lung cancer; PD-L1 = programmed cell death ligand 1.

**Table 1** Baseline Patient Characteristics and Demographic Characteristics

| | Current (All; n = 4240) | Historical (n = 2357) | *P* | Current 2L Anti–PD-L1 (n = 2071) | Current 2L Non-Anti–PD-L1 (n = 2169) | *P* |
|---|---|---|---|---|---|---|
| **Male Sex, n (%)** | 2285 (53.9) | 1319 (56.0) | .1057 | 1154 (55.7) | 1131 (52.1) | .0195 |
| **Mean Age at Index (SD), Years** | 67.5 (9.5) | 66.3 (9.4) | <.0001 | 68.0 (9.4) | 67.0 (9.5) | .0007 |
| **Age Group at Index, n (%)** | | | <.0001 | | | .0049 |
| <65 Years | 1593 (37.6) | 927 (39.3) | | 727 (35.1) | 866 (39.9) | |
| 65-74 Years | 1555 (36.7) | 937 (39.8) | | 785 (37.9) | 770 (35.5) | |
| ≥ 75 Years | 1092 (25.8) | 493 (20.9) | | 559 (27.0) | 533 (24.6) | |
| **Race, n (%)** | | | .2649 | | | <.0001 |
| White/Caucasian | 2839 (67.0) | 1617 (68.6) | | 1411 (68.1) | 1428 (65.8) | |
| Black or African American | 387 (9.1) | 200 (8.5) | | 175 (8.5) | 212 (9.8) | |
| Asian | 97 (2.3) | 37 (1.6) | | 33 (1.6) | 64 (3.0) | |
| Other | 460 (10.8) | 254 (10.8) | | 195 (9.4) | 265 (12.2) | |
| Missing | 457 (10.8) | 249 (10.6) | | 257 (12.4) | 200 (9.2) | |
| **Geographic Regions, n (%)** | | | <.0001 | | | .0002 |
| South | 1580 (37.3) | 1011 (42.9) | | 741 (35.8) | 839 (38.7) | |
| Northeast | 957 (22.6) | 534 (22.7) | | 473 (22.8) | 484 (22.3) | |
| Midwest | 885 (20.9) | 423 (17.9) | | 487 (23.5) | 398 (18.3) | |
| West | 602 (14.2) | 306 (13.0) | | 276 (13.3) | 326 (15.0) | |
| Other territory | 39 (0.9) | 12 (0.5) | | 12 (0.6) | 27 (1.2) | |
| Missing | 177 (4.2) | 71 (3.0) | | 82 (4.0) | 95 (4.4) | |
| **Smoking Status, n (%)** | | | <.0001 | | | <.0001 |
| History of smoking | 3779 (89.1) | 2064 (87.6) | | 1899 (91.7) | 1880 (86.7) | |
| No history of smoking | 444 (10.5) | 224 (9.5) | | 163 (7.9) | 281 (13.0) | |
| Not reported | 17 (0.4) | 69 (2.9) | | 9 (0.4) | 8 (0.4) | |
| **Disease Stage at Diagnosis, n (%)** | | | .0064 | | | .0035 |
| I-IIIA | 668 (15.8) | 360 (15.3) | | 324 (15.6) | 344 (15.9) | |
| IIIB-IV | 3504 (82.6) | 1938 (82.2) | | 1712 (82.7) | 1792 (82.6) | |
| NR | 68 (1.6) | 59 (2.5) | | 35 (1.7) | 33 (1.5) | |
| **ECOG PS Available, n (%)** | 2610 (61.6%) | 877 (37.2%) | <.0001 | 1394 (67.3) | 1216 (56.1) | <.0001 |
| **ECOG PS at Index, n (%)**[a] | n = 2610 | n = 877 | .0131 | n = 1390 | n = 1216 | .0165 |
| 0 | 622 (23.8) | 258 (29.4) | | 300 (21.5) | 322 (26.5) | |
| 1 | 1290 (49.4) | 403 (46.0) | | 694 (49.8) | 596 (49.0) | |
| 2 | 576 (22.1) | 176 (20.1) | | 330 (23.7) | 246 (20.2) | |
| 3 | 117 (4.5) | 40 (4.6) | | 66 (4.7) | 51 (4.2) | |
| 4 | 5 (0.2) | — | | 4 (0.3) | 1 (0.1) | |
| **Follow-up From Index, Months** | | | | | | |
| Mean (SD) | 8.6 (8.0) | 11.0 (14.4) | .497 | 7.4 (6.9) | 9.8 (8.7) | <.0001 |
| Median (range) | 6.3 (0.03-34.8) | 5.4 (0.03-76.9) | | 5.7 (0.03-32.5) | 6.9 (0.03-34.8) | |
| **Patients With <12 Months of Follow-up, n (%)** | 3078 (72.6) | 1699 (72.1) | .6562 | 1623 (78.4) | 1455 (67.1) | <.0001 |
| **Histology, n (%)** | | | .0398 | | | <.0001 |
| Squamous | 1114 (26.3) | 612 (26.0) | | 650 (31.4) | 464 (21.4) | |
| Nonsquamous | 2944 (69.4) | 1611 (68.3) | | 1323 (63.9) | 1621 (74.7) | |
| NOS | 182 (4.3) | 134 (5.7) | | 98 (4.7) | 84 (3.9) | |

**Table 1** Continued

| | Current (All; n = 4240) | Historical (n = 2357) | P | Current 2L Anti–PD-L1 (n = 2071) | Current 2L Non-Anti–PD-L1 (n = 2169) | P |
|---|---|---|---|---|---|---|
| ***EGFR* Mutation, n (%)** | | | | | | |
| Tested | 2889 (68.1) | 1238 (52.5) | <.0001 | 1377 (66.5) | 1512 (69.7) | .0245 |
| Positive | 248 (8.6) | 109 (8.8) | .1053 | 53 (3.8) | 195 (12.9) | <.0001 |
| ***ALK* Translocation, n (%)** | | | | | | |
| Tested | 2786 (65.7) | 1151 (48.8) | <.0001 | 1330 (64.2) | 1456 (67.1) | .0462 |
| Positive | 62 (2.2) | 37 (3.2) | <.0001 | 13 (1.0) | 49 (3.4) | <.0001 |
| **PD-L1 Expression, n (%)** | | | | | | |
| Tested | 997 (23.5) | 35 (1.5) | <.0001 | 581 (28.1) | 416 (19.2) | <.0001 |
| Positive | 248 (24.9) | 12 (34.3) | .4378 | 162 (27.9) | 86 (20.7) | <.0001 |
| ***KRAS* Mutation, n (%)** | | | | | | |
| Tested | 1249 (29.5) | 452 (19.2) | <.0001 | 662 (32.0) | 587 (27.1) | .0005 |
| Positive | 352 (28.2) | 122 (27.0) | <.0001 | 191 (28.9) | 161 (27.4) | .8116 |
| ***ROS1* Translocation, n (%)** | | | | | | |
| Tested | 1714 (40.4) | 160 (6.8) | <.0001 | 892 (43.1) | 822 (37.9) | .0006 |
| Positive | 13 (0.8) | 1 (0.6) | .0673 | 5 (0.6) | 8 (1.0) | .4444 |

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; 2L = second-line; NOS = not otherwise specified; PD-L1 = programmed cell death ligand 1.
[a]Percentages are on the basis of the number of patients with a reported ECOG PS value as the denominator and not the entire sample.

therapies appeared to increase over time during the study period (see Supplemental Figure 1 in the online version). Median duration of follow-up from index was 5.7 (range, 0.03-32.5) months in the current 2L anti–PD-L1 subgroup and 6.9 (range, 0.03-34.8) months in the current 2L non-anti–PD-L1 subgroup. Most (n = 1,842 [88.9%]) of the current group of patients who received 2L anti–PD-L1 therapies were administered nivolumab (n = 186 [9.0%] received pembrolizumab and n = 38 [1.8%] received atezolizumab). Of the 2071 current patients who received 2L anti–PD-L1 therapies, 180 patients (8.7%) received another anti–PD-L1 therapy in the 3L setting (nivolumab, n = 141; pembrolizumab, n = 34; atezolizumab, n = 5). Of note, nearly half of the patients in the current 2L non-anti–PD-L1 subgroup went on to receive anti–PD-L1 agents in the 3L setting (nivolumab: n = 522 [44.0%]; pembrolizumab: n = 29 [2.4%]; atezolizumab: n = 16 [1.3%]). The distribution of age group, race, smoking status, and geographic region at index were statistically different between current 2L anti–PD-L1 and current 2L non-anti–PD-L1 subgroups, although these differences were likely not clinically relevant. A slightly larger percentage of patients who received 2L anti–PD-L1 were male (n = 1,154 [55.7%] vs. n = 1,131 [52.1%]; $P = .0195$), older at index (68.0 years vs. 67.0 years; $P = .0007$), had been assessed for ECOG PS at index (n = 1,394 [67.3%] vs. n = 1,216 [56.1%]; $P < .0001$), and had worse PS (ECOG PS 2-4: n = 400 [28.7%] vs. n = 298 [24.5%]; $P = .0159$) than patients who received 2L non-anti–PD-L1 therapies. There was no significant difference in the distribution of disease stage at diagnosis between these subgroups. Logistic regression of baseline variables and disease characteristics showed that patients were more likely to receive 2L anti–PD-L1 therapy if they had ECOG PS 2-4 (vs. 0-1) or squamous disease, or if they had no *EGFR*, *ALK*, or *ROS1* mutations (Table 3).

### *Second-Line Clinical Outcomes*

Unadjusted median OS from start of 2L treatment was higher for patients in the current cohort (9.4 months) compared with patients in the historical cohort (7.3 months; unadjusted HR, 0.80; 95% confidence interval [CI], 0.76-0.85; Figure 2A). After adjusting for baseline variables, the Cox regression showed an estimated 15% reduction in the risk of death in the current cohort versus the historical cohort (HR, 0.85; 95% CI, 0.80-0.91; see Supplemental Table 2 in the online version). Several baseline variables were associated with increased risk of mortality including sex, race, disease stage, ECOG PS, and biomarker status. Median duration of 2L therapy, estimated using Kaplan–Meier analysis, was longer among patients in the current cohort (3.6 months) than in the historical cohort (2.8 months) (HR, 0.74; 95% CI, 0.69-0.79). Landmark survival was higher at 6, 12, and 24 months in the current cohort (62.3%, 43.5%, and 25.7%, respectively) than in the historical cohort (56.7%, 35.2%, and 17.6%, respectively).

When assessing patients with nonsquamous disease, median OS was 10.2 months in the current cohort and 7.8 months in the historical cohort (unadjusted HR, 0.80; 95% CI, 0.74-0.86); in patients with squamous disease, median OS was 8.3 months in the current cohort and 6.5 months in the historical cohort (unadjusted HR, 0.77; 95% CI, 0.69-0.86; Figure 2B and C). The median OS of patients with nonsquamous histology and *EGFR* mutations was similar in the current cohort (n = 231: 14.9 months) and the historical cohort (n = 103: 17.3 months; unadjusted HR, 1.06; 95% CI, 0.79-1.43).

## Discussion

To the authors' knowledge, this is the first large real-world data analysis of the effect of 2L anti–PD-L1 agents on patients with advanced/metastatic NSCLC after receiving platinum doublet in the 1L. In this early assessment using data from oncology clinics broadly representative of the United States, we see that the adoption of anti–PD-L1 agents in clinical practice was quite rapid: > 50% of patients in the current cohort received anti–PD-L1 agents in the 2L. Although not all patients received an anti–PD-L1 agent, the

**Table 2** Treatments Received in Second and Third Observed Lines of Therapy (≥5% of Patients in at Least 1 Group)

| | Historical | | Current | | Current Anti—PD-L1 | | Current Non-Anti—PD-L1 | |
|---|---|---|---|---|---|---|---|---|
| | 2L (n = 2357) | 3L (n = 1123) | 2L (n = 4240) | 3L (n = 1875) | 2L (n = 2071) | 3L (n = 689) | 2L (n = 2169) | 3L (n = 1186) |
| **Received Treatment After 1L, %** | 100 | 47.6 | 100 | 44.2 | 100 | 33.3 | 100 | 54.7 |
| **Anti—PD-L1, %** | — | 1.2 | 48.8 | 39.9 | 100[a] | 26.1 | — | 47.7 |
| Nivolumab | — | 0.9 | 43.4 | 35.4 | 88.9 | 20.5 | — | 44.0 |
| Pembrolizumab | — | 0.3 | 4.4 | 3.4 | 9.0 | 4.9 | — | 2.4 |
| Atezolizumab | — | — | 0.9 | 1.1 | 1.8 | 0.7 | — | 1.3 |
| **Pemetrexed, %** | 19.0 | 12.8 | 9.6 | 6.8 | — | 5.1 | 18.8 | 7.8 |
| **Docetaxel, %** | 13.6 | 10.8 | 3.3 | 6.3 | — | 11.9 | 6.5 | 3.0 |
| **Anti-EGFR, %[b]** | 12.2 | 19.7 | 6.2 | 11.4 | — | 6.1 | 12.3 | 14.5 |
| **Carboplatin and Paclitaxel, %** | 9.2 | 7.1 | 6.9 | 3.5 | — | 5.2 | 13.5 | 2.4 |
| **Gemcitabine, %** | 8.7 | 11.5 | 2.9 | 6.2 | — | 10.7 | 5.8 | 3.6 |
| **Carboplatin and Pemetrexed, %** | 4.3 | 1.9 | 3.4 | 2.2 | — | 2.8 | 6.7 | 1.9 |
| **Paclitaxel, %** | 4.3 | 5.5 | 1.4 | 3.6 | — | 6.2 | 2.7 | 2.0 |
| **Vinorelbine, %** | 2.9 | 8.7 | 0.7 | 2.5 | — | 4.1 | 1.3 | 1.6 |
| **Docetaxel and Ramucirumab, %** | — | — | 2.0 | 4.7 | — | 9.6 | 4.0 | 1.9 |

Abbreviations: EGFR = epidermal growth factor receptor; 1L = first-line; 2L = second-line; 3L = third-line; PD-L1 = programmed cell death ligand 1.
[a]Three patients in the current cohort received 2L anti—PD-L1 therapies in combination with systemic therapies.
[b]Anti-EGFR therapies: erlotinib, afatinib, gefitinib, osimertinib, imatinib.

**Table 3** Odds Ratios for Likelihood of Receiving 2L Anti–PD-L1 Therapy[a]

| | OR (95% CI) | *P* |
|---|---|---|
| **Male vs. Female Sex** | 1.08 (0.96-1.22) | .1832 |
| **Age** | | |
| ≥75 vs. <65 years | 1.26 (1.07-1.49) | .0778 |
| **No History of Smoking vs. History of Smoking** | 0.82 (0.66-1.01) | .297 |
| **ECOG PS** | | |
| 2-4 vs. 0-1 | 1.24 (1.05-1.47) | <.0001 |
| Missing vs. 0-1 | 0.71 (0.62-0.81) | <.0001 |
| **Tumor Characteristics** | | |
| NOS vs. nonsquamous | 1.32 (0.98-1.76) | .9719 |
| Squamous vs. nonsquamous | 1.71 (1.47-2.00) | <.0001 |
| No *EGFR* mutation vs. *EGFR* mutation | 3.93 (2.89-5.34) | <.0001 |
| No *ALK* mutation vs. *ALK* mutation | 4.02 (2.21-7.33) | .0006 |
| No *KRAS* mutation vs. *KRAS* mutation | 1.06 (0.83-1.35) | .1606 |
| No *ROS1* mutation vs. *ROS1* mutation | 2.57 (0.86-7.72) | .0217 |

Sample includes all patients identified as having received 2L therapy in the study period (n = 8597), including patients who received 2L treatment between January 1, 2014 and December 31, 2014.
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; 2L = second-line; NOS = not otherwise specified; PD-L1 = programmed cell death ligand 1.
[a]Nonsignificant factors include race, smoking status, disease stage at initial diagnosis, the time from diagnosis to first treatment, and geographic region (with the exception of the Midwest vs. the Northeast; $P = .0012$).

median OS increased by 2 months (approximately 20%) since FDA approval of nivolumab, pembrolizumab, and atezolizumab. These observations were consistent for patients with squamous and nonsquamous histology. Additionally, patients in the current cohort who did not receive 2L anti–PD-L1 therapies were likely to receive anti–PD-L1 therapy in later lines of therapy. Accordingly, we observed that approximately 60% of the current cohort received an anti–PD-L1 agent in either the 2L or 3L setting.

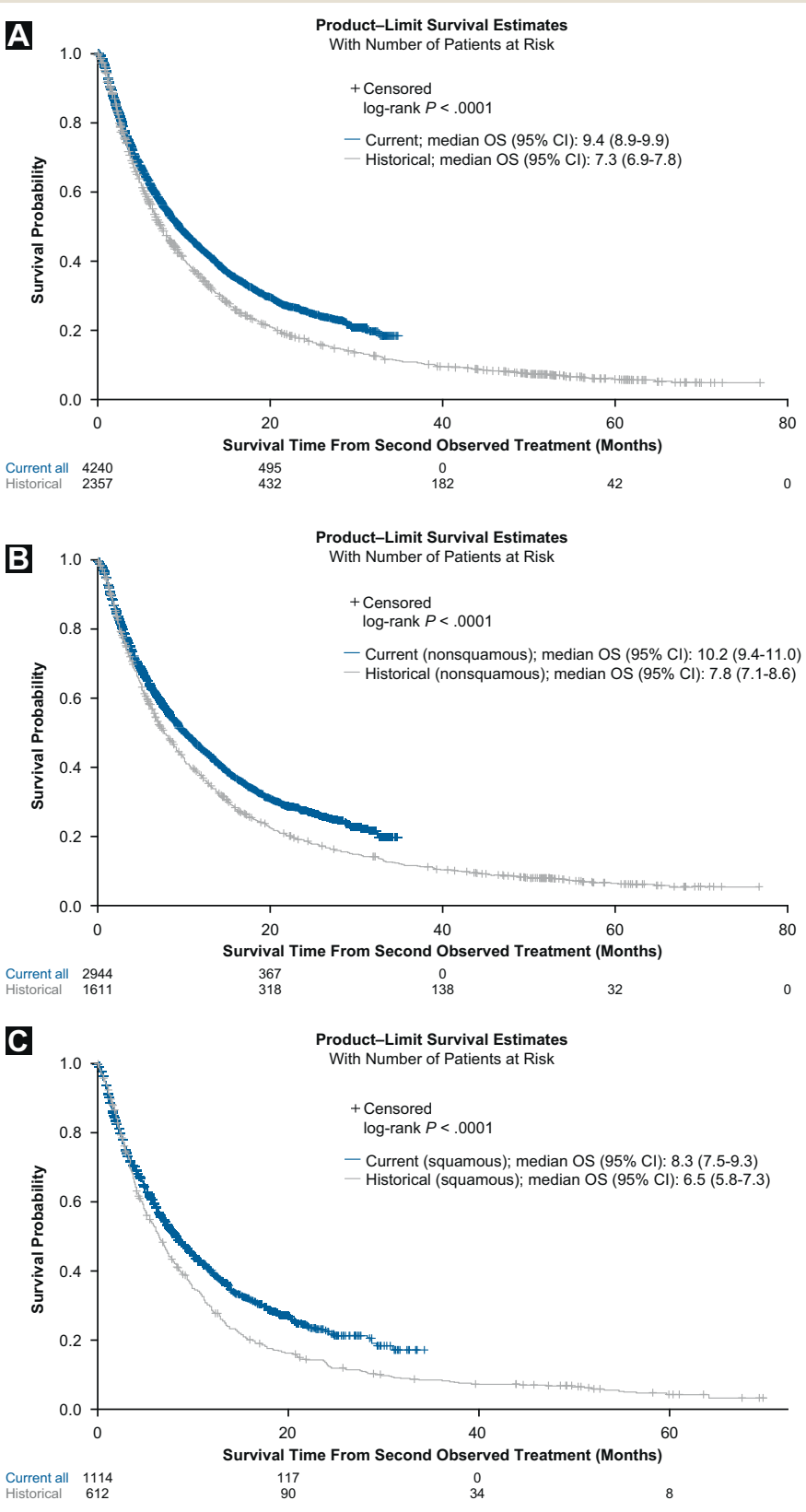
When we compared OS in the current and the historical cohorts, a substantially higher proportion of patients who received platinum-based treatments subsequently received 2L therapy in the contemporary setting than before 2015 (with most receiving nivolumab, which is likely related to its earlier approval date and long market availability). Generally, 2L chemotherapy has been reserved for healthier[22] and younger[23] patients. Therefore, the subgroup of patients who received 2L therapy since the advent of anti–PD-L1 agents might include those who would have been previously precluded from receiving 2L therapy because of their poor health status and limited benefit with previous standard of care. The findings of this study support this observation: patients who received 2L anti–PD-L1 therapies were more likely to have a higher ECOG PS, which is associated with poor prognosis. Anti–PD-L1 therapies have been shown to have fewer toxicity issues and more durable responses than historically available chemotherapy options,[10,12,14] which might improve physician perception of the risk-benefit profile enough to initiate 2L therapy in patients who were previously considered too infirm for 2L chemotherapy. Regardless of the reason for increased usage of 2L chemotherapy in the current cohort, the separation of OS curves and improvement in median OS provides a real-world confirmation of anti–PD-L1 benefits reported in clinical trials. Further follow-up of this cohort would indicate whether usage of PD-L1 therapy in 2L/3L leads to an improvement in long-term survival in the real-world setting similar to that seen in clinical trials of patients with advanced/metastatic NSCLC.[24-26]

Current patients whose tumors tested positive for *EGFR*, *ALK*, and *ROS1* mutations were more likely to receive non-anti–PD-L1 therapies; patients who present with these biomarkers are eligible for targeted therapies and generally have a better prognosis.[27] For example, the National Comprehensive Cancer Network guidelines recommend that patients with NSCLC with an activating *EGFR* mutation should receive treatment with the EGFR tyrosine kinase inhibitors erlotinib, gefitinib, or afatinib.[28] All of these EGFR-targeted treatments were widely available during the historical period used in this study (gefitinib and erlotinib were approved by the FDA in this clinical context in 2004; afatinib in 2013).[27] In this study, the median OS of patients with EGFR-mutant tumors was similar in historical and current cohorts, suggesting that EGFR-targeted therapies received after platinum-based treatment did not substantially contribute to the improved OS observed in the current setting. Testing for relevant biomarkers to help guide treatment decisions was suboptimal in the historical and current cohorts. Although *EGFR* mutation testing occurred in most patients in both cohorts, approximately one-third of patients in community practices are still not undergoing this testing. Likewise, PD-L1 testing was minimal in the historical cohort, increasing to 23.5% of patients with a PD-L1 test result in the current cohort. Recent evidence suggests that, along with the increase in immune checkpoint inhibitors, recognition of the need for PD-L1 testing has increased.[29]

This study assessed a relatively large cohort of patients who received 2L therapy for NSCLC using the Flatiron Health database; Flatiron demographic characteristics are generally similar to those of the Surveillance, Epidemiology, and End Results program.[30] The Flatiron Health database has previously been used to assess real-world data in patients with NSCLC,[3,31] and a previous analysis of a broader and larger population of patients with NSCLC reported baseline demographic and disease characteristics similar to those in the present study.[32] OS among patients with squamous disease in the historical cohort was in line with that reported using a different observational data source.[15] Patients in a real-world setting generally have a poorer prognosis than those in clinical trials; despite this, the introduction of anti–PD-L1 agents appears to have provided clear clinical benefit to patients who receive therapy in routine clinical practice.

This analysis has several limitations. Data for some variables (eg, ECOG PS) were incomplete, and some patient characteristics were either not recorded (such as Charlson Comorbidity Index) or only partially recorded (such as PD-L1 expression) in the Flatiron Health database. Although we found no evidence of a systematic difference in patient and disease baseline characteristics between patients who did and who did not have available ECOG PS data, we cannot exclude the possibility of selection bias. Additionally, the electronic health records in the Flatiron Health database do not capture adverse event data in their structured data. We therefore cannot assess the effect of the introduction of anti–PD-L1 agents on tolerability during 2L and 3L therapy of NSCLC. The Flatiron Health database includes data obtained during treatment at participating clinics and health care providers only, and consequently lacks data relating to treatments received at nonparticipating

**Figure 2** Kaplan–Meier Curves for: (A) Current Versus Historical Cohorts; (B) Current Nonsquamous Versus Historical Nonsquamous Subgroups; and (C) Current Squamous Versus Historical Squamous Subgroups




Abbreviation: OS = overall survival.

centers. Therefore, lines of treatment are described in this report as "observed lines." Last, because of the relatively recent approvals of anti—PD-L1 therapies for NSCLC, follow-up is relatively short in this analysis. Future analysis of this cohort is planned to examine whether real-world use of these therapies in clinical practice replicates the long-term durable survival observed in clinical trial settings.[24,33-35]

## Conclusion

In summary, survival of patients receiving 2L therapy for NSCLC in routine US clinical practice has significantly improved since the introduction of anti—PD-L1 therapies, regardless of tumor histology. A greater proportion of patients with advanced/metastatic NSCLC received 2L therapy in the contemporary clinical setting than pre-2014, which might suggest that anti—PD-L1 therapy has enabled access to treatment for patients who would previously have been considered too infirm to receive 2L therapy.

### *Clinical Practice Points*

- Very few publications report real-world data on 2L therapy for NSCLC, and the effect of anti—PD-L1 therapies on survival is unclear; only recently has sufficiently mature real-world data been available to assess this.
- We found that patients who had previously received 1L platinum-based therapy for NSCLC were more likely to receive 2L therapy in contemporary clinical practice (current cohort, 57% of patients) than in routine clinical practice before the approval of anti—PD-L1 therapies (historical cohort, 37% of patients).
- Patients in contemporary clinical practice were more likely to receive 2L anti—PD-L1 therapy if they had poorer ECOG PS, squamous histology, or no *EGFR*, *ALK*, or *ROS1* mutations.
- Unadjusted median OS from start of 2L therapy was significantly longer in the current cohort (9.4 months) compared with the historical cohort (7.3 months); after adjusting for baseline variables, the risk of death was significantly decreased by 15% in the current cohort.
- Since the approval of anti—PD-L1 therapies, patients are more likely to receive 2L therapy and have longer survival than patients who received care before approval of anti—PD-L1 therapies.

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## Disclosure

Lee Schwartzberg has had consulting/advisory relationships with Eisai, Helsinn, Merck, and Tesaro, and has received research funding from Helsinn. Beata Korytowsky, John R. Penrod, Ying Zhang, T. Kim Le, and Lee Krug are employees of, and hold stock in, Bristol-Myers Squibb. Cory Batenchuk was an employee of Bristol-Myers Squibb at the time of study initiation and data analysis.

## Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2019.04.004.

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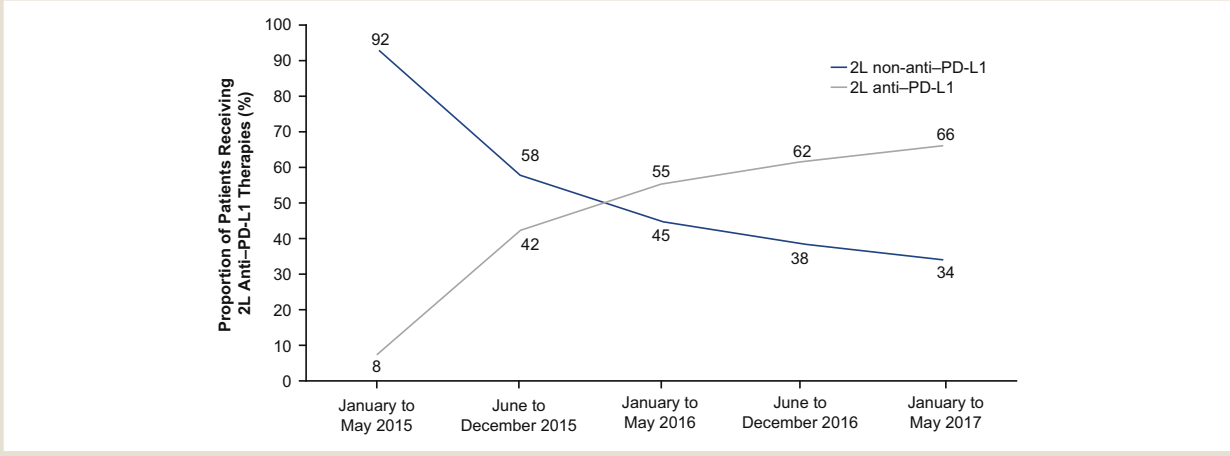
## Supplemental Data

**Supplemental Figure 1** Uptake of Anti–PD-L1 and Non-Anti–PD-L1 Therapies From January 2015 to May 2017




Abbreviations: 2L = second-line; PD-L1 = programmed cell death ligand 1.

**Supplemental Table 1** Oncogenic Testing According to Cohort

| | Historical (n = 2357) | Current (All; n = 4240) | Current 2L Anti–PD-L1 (n = 2071) | Current 2L Non-Anti–PD-L1 (n = 2169) | Current 2L (All) vs. Historical *P* Value | Current 2L Anti–PD-L1 vs. Historical *P* Value | Current 2L Anti–PD-L1 vs. Current 2L Non-Anti–PD-L1 *P* Value |
|---|---|---|---|---|---|---|---|
| ***EGFR*** | | | | | | | |
| Patients tested | 1238 (52.5) | 2889 (68.1) | 1377 (66.5) | 1512 (69.7) | <.0001 | <.0001 | .0245 |
| Test used[a] | | | | | <.0001 | <.0001 | <.0001 |
| FISH | 1 (0.1) | 2 (0.1) | 2 (0.1) | – | | | |
| IHC | – | 3 (0.1) | 1 (0.1) | 2 (0.1) | | | |
| NGS | 78 (6.3) | 773 (26.8) | 430 (31.2) | 343 (22.7) | | | |
| PCR | 736 (59.5) | 1089 (37.7) | 469 (34.1) | 620 (41.0) | | | |
| Other | 182 (14.7) | 53 (18.6) | 247 (17.9) | 290 (19.2) | | | |
| Unknown | 243 (19.6) | 492 (17.0) | 230 (16.7) | 262 (17.3) | | | |
| Mutations present | 109 (8.8) | 248 (8.6) | 53 (3.8) | 195 (12.9) | .1053 | <.0001 | <.0001 |
| ***ALK*** | | | | | | | |
| Patients tested | 1151 (48.8) | 2786 (65.7) | 1330 (64.2) | 1456 (67.1) | <.0001 | <.0001 | .0462 |
| Test used[a] | | | | | <.0001 | <.0001 | .0001 |
| FISH | 859 (74.6) | 1707 (61.3) | 764 (57.4) | 943 (64.8) | | | |
| IHC | 6 (0.5) | 82 (2.9) | 42 (3.2) | 40 (2.7) | | | |
| NGS | 51 (4.4) | 592 (21.2) | 330 (24.8) | 262 (18.0) | | | |
| PCR | 107 (9.3) | 135 (4.8) | 63 (4.7) | 72 (4.9) | | | |
| Other | 4 (0.3) | 23 (0.8) | 16 (1.2) | 7 (0.5) | | | |
| Unknown | 134 (11.6) | 300 (10.8) | 137 (10.3) | 163 (11.2) | | | |
| Translocation present | 37 (3.2) | 62 (2.2) | 13 (1.0) | 49 (3.4) | <.0001 | <.0001 | <.0001 |
| **PD-L1** | | | | | | | |
| Patients tested | 35 (1.5) | 997 (23.5) | 581 (28.1) | 416 (19.2) | <.0001 | <.0001 | <.0001 |
| Test used[a] | | | | | .5234 | .3876 | .1850 |
| IHC | 28 (80.0) | 878 (88.1) | 505 (86.9) | 373 (89.7) | | | |
| Mass spectrometry | – | 3 (0.3) | 1 (0.2) | 2 (0.5) | | | |
| PCR | – | 10 (1.0) | 9 (1.5) | 1 (0.2) | | | |
| Other | 1 (2.9) | 14 (1.4) | 9 (1.5) | 5 (1.2) | | | |
| Unknown | 6 (17.1) | 95 (9.5) | 59 (10.2) | 36 (8.7) | | | |
| PD-L1 expression | 12 (34.3) | 248 (24.9) | 162 (27.9) | 86 (20.7) | .4378 | .7689 | <.0001 |
| ***KRAS*** | | | | | | | |
| Patients tested | 452 (19.2) | 1249 (29.5) | 662 (32.0) | 587 (27.1) | <.0001 | <.0001 | .0005 |
| Test used[a] | | | | | <.0001 | <.0001 | .3980 |

**Supplemental Table 1** Continued

| | Historical (n = 2357) | Current (All; n = 4240) | Current 2L Anti–PD-L1 (n = 2071) | Current 2L Non-Anti–PD-L1 (n = 2169) | Current 2L (All) vs. Historical *P* Value | Current 2L Anti–PD-L1 vs. Historical *P* Value | Current 2L Anti–PD-L1 vs. Current 2L Non-Anti–PD-L1 *P* Value |
|---|---|---|---|---|---|---|---|
| NGS | 72 (15.9) | 756 (60.5) | 415 (62.7) | 341 (58.1) | | | |
| PCR | 237 (52.4) | 288 (23.1) | 143 (21.6) | 145 (24.7) | | | |
| Other | 73 (16.2) | 86 (6.9) | 45 (6.8) | 41 (7.0) | | | |
| Unknown | 71 (15.7) | 119 (9.5) | 59 (8.9) | 60 (10.2) | | | |
| Mutations present | 122 (27.0) | 352 (28.2) | 191 (28.9) | 161 (27.4) | <.0001 | <.0001 | .8116 |
| ***ROS1*** | | | | | | | |
| Patients tested | 160 (6.8) | 1714 (40.4) | 892 (43.1) | 822 (37.9) | <.0001 | <.0001 | .0006 |
| Test used[a] | | | | | .1661 | .0368 | .0228 |
| FISH | 105 (65.6) | 947 (55.3) | 457 (51.2) | 490 (59.6) | | | |
| IHC | – | 14 (0.8) | 7 (0.8) | 7 (0.9) | | | |
| NGS | 42 (26.3) | 564 (32.9) | 318 (35.7) | 246 (29.9) | | | |
| PCR | 1 (0.6) | 32 (1.9) | 21 (2.4) | 11 (1.3) | | | |
| Other | 1 (0.6) | 22 (1.3) | 13 (1.5) | 9 (1.1) | | | |
| Unknown | 14 (8.8) | 147 (8.6) | 81 (9.1) | 66 (8.0) | | | |
| Translocations present | 1 (0.6) | 13 (0.8) | 5 (0.6) | 8 (1.0) | .0673 | .0494 | .4444 |

Data are presented as n (%) except where otherwise noted.
Abbreviations: FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; 2L = second-line; NGS = next-generation sequencing; PCR = polymerase chain reaction; PD-L1 = programmed cell death ligand 1.
[a]Patients could have had more than 1 test.

**Supplemental Table 2** Cox Regression HRs for Death in Combined Historical and Current Cohorts[a]

| | HR (95% CI) | *P* |
|---|---|---|
| **Current vs. Historical** | 0.85 (0.80-0.91) | <.0001 |
| **Male vs. Female Sex** | 1.25 (1.18-1.32) | <.0001 |
| **Age** | | |
| 65-75 vs. <65 years | 1.04 (0.97-1.12) | .2482 |
| ≥ 75 vs. <65 years | 1.05 (0.97-1.14) | .222 |
| **Race** | | |
| Asian vs. white/Caucasian | 0.70 (0.55-0.89) | .0035 |
| Black/African American vs. white/Caucasian | 0.89 (0.80-0.99) | .0267 |
| Other vs. white/Caucasian | 0.92 (0.84-1.02) | .0975 |
| **Smoking Status** | | |
| No history vs. confirmed history | 0.95 (0.85-1.05) | .3072 |
| **Disease Stage at Diagnosis** | | |
| IIIB-IV vs. I-IIIA | 1.16 (1.07-1.26) | .0003 |
| **ECOG PS** | | |
| 2-4 vs. 0-1 | 1.84 (1.68-2.01) | <.0001 |
| Missing vs. 0-1 | 1.16 (1.09-1.25) | <.0001 |
| **Tumor Characteristics** | | |
| NOS vs. nonsquamous | 1.24 (1.09-1.42) | .0011 |
| Squamous vs. Nonsquamous | 0.97 (0.91-1.05) | .4923 |
| No *EGFR* mutation vs. *EGFR* mutation | 1.29 (1.11-1.48) | .0007 |
| No *ALK* mutation vs. *ALK* mutation | 1.60 (1.23-2.10) | .0006 |
| No *KRAS* mutation vs. *KRAS* mutation | 0.80 (0.70-0.91) | .0009 |
| No *ROS1* mutation vs. *ROS1* mutation | 0.89 (0.44-1.79) | .7376 |

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; NOS = not otherwise specified.
[a]Nonsignificant factors include the time from diagnosis to first treatment and geographic region (with the exception of other territory vs. the Northeast; $P < .0001$).