Original Article

# Real-World Progression, Treatment, and Survival Outcomes During Rapid Adoption of Immunotherapy for Advanced Non–Small Cell Lung Cancer

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**BACKGROUND:** Despite the rapid adoption of immunotherapies in advanced non–small cell lung cancer (advNSCLC), knowledge gaps remain about their real-world (rw) performance. **METHODS:** This retrospective, observational, multicenter analysis used the Flatiron Health deidentified electronic health record-derived database of rw patients with advNSCLC who received treatment with PD-1 and/or PD-L1 (PD-[L]1) inhibitors before July 1, 2017 (N = 5257) and had ≥6 months of follow-up. The authors investigated PD-(L)1 line of treatment and PD-L1 testing rates and the relationship between overall survival (OS) and rw intermediate endpoints: progression-free survival (rwPFS), rw time to progression (rwTTP), rw time to next treatment (rwTTNT), and rw time to discontinuation (rwTTD). **RESULTS:** First-line PD-(L)1 inhibitor use increased from 0% (in the third quarter of 2014 [Q3 2014]) to 42% (Q2 2017) over the study period. PD-L1 testing also increased (from 3% in Q3 2015 to 70% in Q2 2017). The estimated median OS was 9.3 months (95% CI, 8.9-9.8 months), and the estimated rwPFS was 3.2 months (95% CI, 3.1-3.3 months). Longer OS and rwPFS were associated with ≥50% PD-L1 percentage staining results. Correlations (ρ) between OS and intermediate endpoints were ρ = 0.75 (95% CI, 0.73-0.76) for rwPFS and ρ = 0.60 (95% CI, 0.57-0.63) for rwTTP, and, for treatment-based intermediate endpoints, correlations were ρ = 0.60 (95% CI, 0.56-0.64) for rwTTNT (N = 856) and ρ = 0.81 (95% CI, 0.80-0.82) for rwTTD. **CONCLUSIONS:** The use of first-line PD-(L)1 inhibitors and PD-L1 testing has substantially increased, with better outcomes for patients who have ≥50% PD-L1 percentage staining. Intermediate rw tumor-dynamics estimates were moderately correlated with OS in patients with advNSCLC who received immunotherapy, highlighting the need for optimizing and standardizing rw endpoints to enhance the understanding of patient outcomes outside clinical trials. ***Cancer* 2019;125:4019-4032**. 

**KEYWORDS:** endpoints, immunotherapy, non–small cell lung cancer, PD-1, PD-L1, real-world.

## INTRODUCTION

Over the past 3 years, immunotherapy has changed the treatment paradigm of advanced non–small cell lung cancer (advNSCLC). The pivotal clinical trials that enabled regulatory approvals of these agents used overall survival (OS) and intermediate endpoints such as progression-free survival (PFS) to measure benefit and have focused on highly controlled protocols applied to narrowly defined populations. Studies conducted in patient cohorts from real-world community settings can complement clinical trials by expanding generalizability to under-represented populations and to the complexities and diversity of day-to-day cancer care. These studies leverage real-world data (RWD) captured in electronic health records (EHRs) as both structured (eg, laboratory values) and unstructured (eg, radiology reports) information.[1,2] Analyzing those sources to create real-world evidence, however, necessitates specific approaches for abstracting endpoints (ie, real-world PFS [rwPFS]), accounting for differences between clinical trials and real-world practice and documentation patterns. For example, descriptions of progression on imaging reports may bypass Response Evaluation Criteria in Solid Tumors (RECIST)[3] language. Contemporary and robust real-world evidence is crucial for helping clinicians tailor new treatments, such as immunotherapy, to real-world patients with advNSCLC.

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This study expands our prior investigation of real-world patients with advNSCLC who received treatment with nivolumab or pembrolizumab (both PD-1 inhibitors),[4] conducted during the early adoption period after the initial approval in advNSCLC (both as the second or higher therapy line; nivolumab for patients with squamous histology tumors, and pembrolizumab for patients with PD-L1–expressing tumors).[5-8] Since that study, 1) 4 additional approvals in advNSCLC have been granted to 3 different anti-PD-(L)1 therapies; 2) the number of patients treated with PD-(L)1 inhibitors and the follow-up period have substantially increased; 3) scientific understanding of PD-L1 testing has matured; 4) management has changed, including the practice of treating beyond RECIST-defined progression based on the continued benefit observed in some cases after early "pseudoprogression" because of inflammatory response; and 5) recognition of the importance of progression and treatment-based intermediate endpoints for patients has grown.[8-12] Other drug approvals in the United States during this period, particularly for patients with *EGFR* mutations and *ALK* rearrangements, have also improved outcomes and treatment tolerability for patients with advNSCLC.[13] These shifts underscore both the challenge and the urgency for assessing immunotherapy using real-world endpoints.

In this study of a large contemporary cohort of patients with advNSCLC who received treatment with PD-(L)1 inhibitors at a time of rapid immunotherapy adoption, we evaluated real-world progression and treatment-based intermediate endpoints, strengthening prior analyses (and increasing generalizability) by adding almost 4000 patients (nearly a 4-fold increase) and doubling the observation time.

## MATERIALS AND METHODS

### *Study Design*

This retrospective, observational, multicenter analysis used EHR-derived data collected during routine care of real-world patients with advNSCLC who received PD-(L)1 inhibitors with a 3-fold objective: 1) describe real-world PD-(L)1 inhibitor treatment and testing patterns as well as patient characteristics; 2) evaluate OS and real-world progression-free survival (rwPFS) overall and by characteristics that may be associated with outcomes; and 3) understand the relationship between OS and other real-world intermediate endpoints, including real-world progression and treatment-based outcomes. The study period was January 1, 2011 through December 31, 2017. Institutional Review Board approval was obtained. Informed consent was waived by the Institutional Review Board because this was a retrospective, noninterventional study using routinely collected data.

### *Data Sources*

For this study, we used data from the Flatiron Health longitudinal EHR-derived database, which represented over 265 US cancer clinics, including more than 2 million patients with cancer overall and 120,000 patients who had a structured International Classification of Diseases code for lung cancer and a visit on or after January 1, 2011, at the time of data set generation. Data were gathered in a manner that was agnostic to the source EHR and were stored centrally by Flatiron Health in a secure manner, compliant with relevant privacy laws and regulations. To prepare EHR content for analysis, structured data were harmonized and normalized to a standard ontology, whereas unstructured data were extracted from EHR-based digital documents through technology-enabled chart abstraction.[2] Data provided to third parties were de-identified, and provisions were in place to prevent re-identification in order to protect patients' confidentiality.

Biomarker information was abstracted from unstructured EHR biomarker testing or pathology reports and, when those sources were not available, oncology clinic visit notes. Details were collected on relevant test type(s), date(s), and result(s). For example, the percentage of cells staining for PD-L1 (categorized for analyses as <1%, 1%-49% and ≥50% based on approved staining thresholds for PD-[L]1 therapy in NSCLC)[14,15] was recorded when available, and PD-L1 status (positive or negative) was also collected if the report provided an interpretation of test results. All data were abstracted exactly as reported and were not derived from other test results.

Patient-level zip codes from the EHR-derived database were linked to the median income estimates available through the 2015 American Community Survey as a proxy for socioeconomic status and categorized by quartiles. Because data available through the American Community Survey provided income at the census tract level, these median estimates were aggregated and weighted based on the number of US households in the census tract area, resulting in national-level, household-adjusted median income quartiles.

### *Cohort Selection*

Cohort eligibility criteria (see Supporting Fig. 1) included having >1 visit to a community oncology clinic documented in the EHR; confirmation of advNSCLC or early-stage

NSCLC with a recurrence or progression (see Supporting Table 1) during the study period through a review of unstructured data (ie, clinical notes, radiology reports, or pathology reports); and initiation of a treatment regimen containing nivolumab, pembrolizumab, or atezolizumab in the advanced setting before July 1, 2017. Patients who had incomplete historical treatment data (ie, >90-day gap between advanced diagnosis and structured activity in the EHR) or multiple primary tumors were excluded. All patients were followed until December 31, 2017, providing the opportunity for ≥6 months of follow-up.

### *Outcome Measures*

Primary study outcome measurements were OS and rwPFS. Correlation of real-world outcomes (rwPFS, real-world time to progression [rwTTP], real-world time to next treatment [rwTTNT], and real-world time to treatment discontinuation [rwTTD]) with OS was also evaluated.

Dates of death were based on a composite mortality variable comprised of structured and unstructured EHR data linked to commercial mortality data and the Social Security Administration's Death Master File; a sample cohort of patients with advNSCLC from a previous analysis yielded a median survival similar to that calculated using the National Death Index as a gold standard.[16] Dates of real-world progression (rwP) events were retrospectively captured from the EHR from clinician notes documenting progression of advNSCLC; methods for curating rwP were previously described and evaluated with a validation framework.[2,17]

Therapy lines for advNSCLC were based on EHR documentation of systemic anticancer treatments and were generated by rule-based algorithms indexed to the patient's advNSCLC diagnosis date. These rules are objective (based on literature, clinical guidelines, and deep clinical experience) and were applied to treatments actually received, irrespective of order sets or care plans (see Supporting Methods). The treatment discontinuation date was the date the patient discontinued the earliest PD-(L)1 inhibitor-containing line regimen (ie, had a subsequent line of therapy, a date of death, or a gap >120 days between the last noncancelled order, administration, or oral drug episode within the PD-[L]1 inhibitor-containing line regimen and last EHR activity).

### *Statistical Analyses*

Descriptive analyses were conducted for patient and disease characteristics stratified by subgroups of interest. Unless otherwise indicated, baseline values such as organ dysfunction are indexed to the date of the earliest PD-(L)1 inhibitor initiation. Continuous variables were compared across subgroups using analyses of variance or Kruskal-Wallis tests when evaluating medians. Categorical variables were compared using the chi-square test or the Fisher exact test when the expected frequency was <5. Cumulative frequencies were used to assess the uptake of PD-(L)1 inhibitor use, PD-L1 testing, and PD-L1 test results (reported status or percentage of cells staining) over time.

OS and rwPFS were compared across predefined demographic and clinical characteristics using the Kaplan-Meier method and the log-rank test. Median survival estimates and unadjusted hazard ratios from Cox proportional hazards models with 95% CIs were reported. All analyses were indexed to the date of the earliest PD-(L)1 inhibitor initiation (first administration or noncancelled order) within the earliest PD-(L)1 inhibitor-containing line of therapy given in the advanced setting (see Supporting Table 1). OS was defined as the time from PD-(L)1 initiation to death, and patients were censored at their last known EHR activity. rwPFS was defined as the time from PD-(L)1 initiation to the first rwP date >14 days after PD-(L)1 inhibitor initiation or to death. rwTTP was defined as the time from PD-(L)1 inhibitor initiation to the first rwP date >14 days after PD-(L)1 inhibitor initiation. Censoring was based on the last clinic note available for rwP assessment.

Real-world treatment-based endpoints were defined as: rwTTNT, the time from PD-(L)1 inhibitor initiation to the start of the line of therapy immediately after the earliest PD-(L)1 inhibitor-containing line; and rwTTD, the time from PD-(L)1 inhibitor initiation to the date the patient discontinued the PD-(L)1 inhibitor-containing line regimen as previously defined.

Correlation of real-world outcomes (rwPFS, rwTTP, rwTTNT, and rwTTD) with OS was assessed at the patient level by calculating the Spearman rank correlation coefficient (ρ) and 95% CIs. The 95% CI for the Spearman ρ was calculated using Fisher z-transformation on the Spearman ρ. When calculating correlations, the cohort was restricted to patients with the event(s) of interest: 1) date of death for rwPFS, 2) date of death and rwP for rwTTP, 3) date of death and a next line of therapy start for rwTTNT, and 4) date of death and discontinuation of the PD-(L)1 inhibitor-containing regimen for rwTTD.

A 2-sided significance level of $\alpha = .05$ was used for all tests of significance. Adjustments were not made for multiple comparisons. All statistical analyses were performed using R, version 3.3.1 (R Foundation for Statistical Computing).

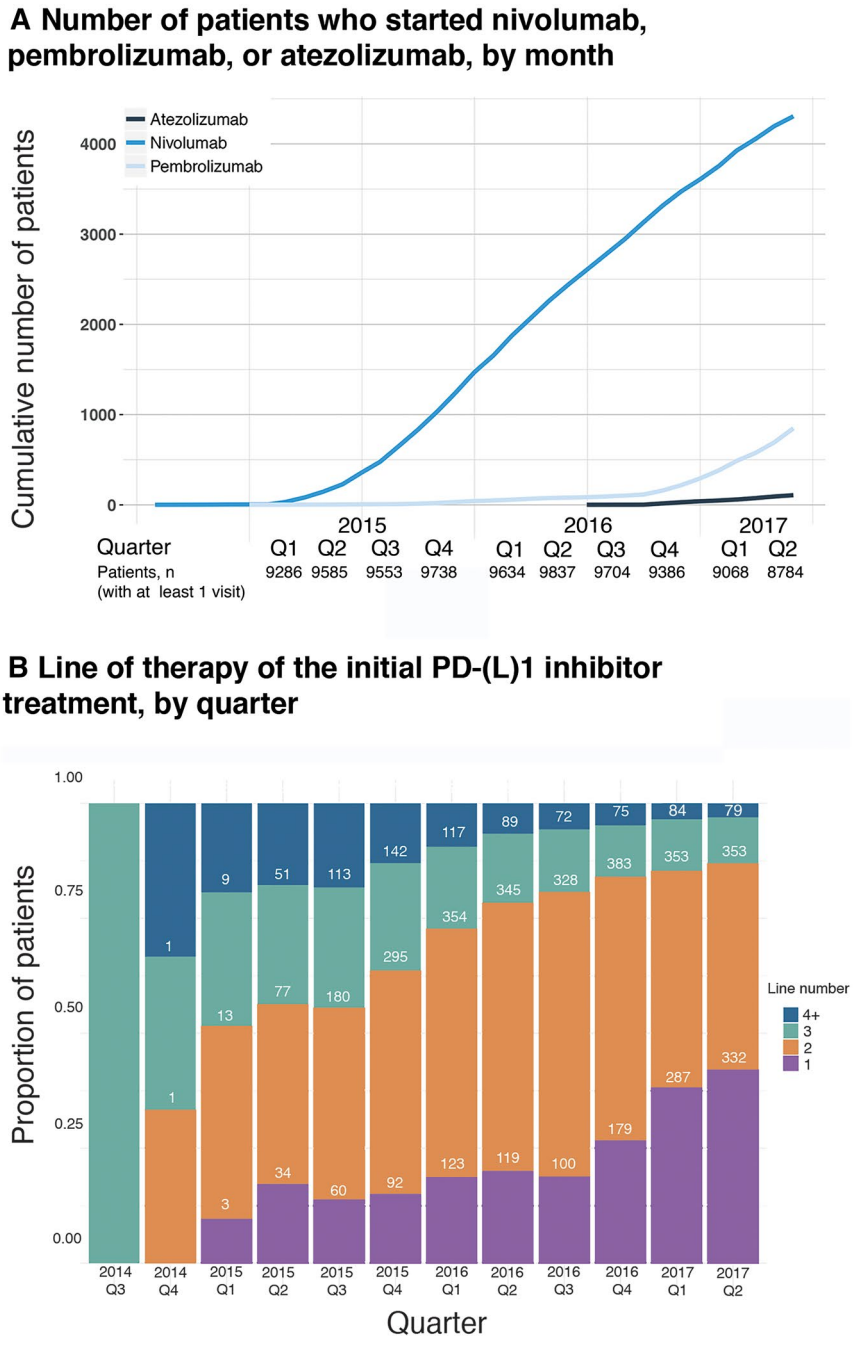


**Figure 1.** (A,B) Uptake of PD-1 and/or PD-L1 (PD-[L]1) inhibitors and changes in treatment line during the study period are illustrated. When the patient's treatment line contained more than 1 PD-(L)1 inhibitor (eg, nivolumab, pembrolizumab), the patient was included in all applicable groups for this analysis; there were 4 patients who received more than 1 PD-(L)1 inhibitor in their index line in this cohort.

## RESULTS

### *Treatment Patterns and Patient Characteristics*

In this cohort (N = 5257), 82% of patients received nivolumab, 16% received pembrolizumab, and 2% received atezolizumab. Uptake of each therapy increased after respective approvals (Fig. 1A). Starting in the fourth quarter of 2015 (Q4 2015), PD-(L)1 inhibitor use in the third or later lines declined but increased in the first line (use in the second line increased only until Q4 2016) (Fig. 1B).

**TABLE 1.** Selected Patient Characteristics for the Overall Cohort, Stratified by Quarter, in Which the Patient Initiated PD-(L)1 Inhibitor Treatment[a]

| Characteristic | Overall, N = 5257 | 2014 Q3, n = 1 | 2014 Q4, n = 3 | 2015 Q1, n = 31 | 2015 Q2, n = 197 | 2015 Q3, n = 432 | 2015 Q4, n = 608 | 2016 Q1, n = 656 | 2016 Q2, n = 592 | 2016 Q3, n = 530 | 2016 Q4, n = 669 | 2017 Q1, n = 750 | 2017 Q2, n = 788 | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age at PD-(L)1 inhibitor initiation: median [IQR], y[b] | 69.0 [62.0;76.0] | 72.0 [72.0;72.0] | 63.0 [62.0;68.0] | 69.0 [60.5;75.0] | 70.0 [63.0;75.0] | 69.0 [60.0;76.0] | 68.0 [60.0;75.0] | 70.0 [61.0;76.0] | 69.0 [61.0;75.0] | 69.0 [63.0;76.0] | 69.0 [62.0;75.0] | 71.0 [63.0;78.0] | 70.0 [61.0;77.0] | .001 |
| Age category at PD-(L)1 inhibitor initiation: Categorical, no. (%)[b] | | | | | | | | | | | | | | .023 |
| ≤49 y | 160 (3.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (2.5) | 17 (3.9) | 25 (4.1) | 18 (2.7) | 13 (2.2) | 13 (2.5) | 18 (2.7) | 28 (3.7) | 23 (2.9) | |
| 50-64 y | 1584 (30.1) | 0 (0.0) | 2 (66.7) | 13 (41.9) | 49 (24.9) | 137 (31.7) | 205 (33.7) | 197 (30.0) | 200 (33.8) | 151 (28.5) | 196 (29.3) | 201 (26.8) | 233 (29.6) | |
| 65-74 y | 1931 (36.7) | 1 (100.0) | 1 (33.3) | 10 (32.3) | 89 (45.2) | 156 (36.1) | 223 (36.7) | 243 (37.0) | 218 (36.8) | 208 (39.2) | 270 (40.4) | 249 (33.2) | 263 (33.4) | |
| ≥75 y | 1582 (30.1) | 0 (0.0) | 0 (0.0) | 8 (25.8) | 54 (27.4) | 122 (28.2) | 155 (25.5) | 198 (30.2) | 161 (27.2) | 158 (29.8) | 185 (27.7) | 272 (36.3) | 269 (34.1) | |
| Group stage at initial diagnosis, no. (%) | | | | | | | | | | | | | | .006 |
| Stage 0 | 1 (<0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) | 0 (0.0) | <4 | 0 (0.0) | |
| Stage I | 385 (7.3) | 0 (0.0) | 0 (0.0) | 5 (16.1) | 13 (6.6) | 31 (7.2) | 38 (6.2) | 52 (7.9) | 45 (7.6) | 34 (6.4) | 50 (7.5) | 63 (8.4) | 54 (6.9) | |
| Stage II | 338 (6.4) | 0 (0.0) | 0 (0.0) | 1 (3.2) | 21 (10.7) | 39 (9.0) | 36 (5.9) | 48 (7.3) | 47 (7.9) | 27 (5.1) | 43 (6.4) | 44 (5.9) | 32 (4.1) | |
| Stage III | 1217 (23.2) | 0 (0.0) | 0 (0.0) | 13 (41.9) | 69 (35.0) | 114 (26.4) | 151 (24.8) | 164 (25.0) | 132 (22.3) | 143 (27.0) | 143 (21.4) | 145 (19.3) | 143 (18.1) | |
| Stage IV | 3159 (60.1) | 1 (100.0) | 3 (100.0) | 11 (35.5) | 89 (45.2) | 229 (53.0) | 365 (60.0) | 375 (57.2) | 354 (59.8) | 314 (59.2) | 413 (61.7) | 471 (62.8) | 534 (67.8) | |
| Not reported | 157 (3.0) | 0 (0.0) | 0 (0.0) | 1 (3.2) | 5 (2.5) | 19 (4.4) | 18 (3.0) | 17 (2.6) | 14 (2.4) | 11 (2.1) | 20 (3.0) | 27 (3.6) | 25 (3.2) | |
| PD-L1 tested on or before starting PD-(L)1 inhibitor, no. (%) | | | | | | | | | | | | | | <.001 |
| Yes | 1502 (28.6) | 0 (0.0) | 0 (0.0) | 2 (6.5) | 5 (2.5) | 13 (3.0) | 63 (10.4) | 70 (10.7) | 83 (14.0) | 109 (20.6) | 211 (31.5) | 394 (52.5) | 552 (70.1) | |
| No | 3755 (71.4) | 1 (100.0) | 3 (100.0) | 29 (93.5) | 192 (97.5) | 419 (97.0) | 545 (89.6) | 586 (89.3) | 509 (86.0) | 421 (79.4) | 458 (68.5) | 356 (47.5) | 236 (29.9) | |
| PD-L1 expression status among those tested, no. (%)[c,d] | | | | | | | | | | | | | | <.001 |
| Positive | 412 (27.4) | 0 (0.0) | 0 (0.0) | 2 (100.0) | 1 (20.0) | 7 (53.8) | 31 (49.2) | 31 (44.3) | 32 (38.6) | 41 (37.6) | 75 (35.5) | 96 (24.4) | 96 (17.4) | |
| Negative/not detected | 450 (30.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (20.0) | 3 (23.1) | 24 (38.1) | 29 (41.4) | 41 (49.4) | 54 (49.5) | 63 (29.9) | 79 (20.1) | 156 (28.3) | |
| Equivocal | 5 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.6) | 2 (2.9) | 1 (1.2) | 0 (0.0) | 1 (0.5) | 0 (0.0) | 0 (0.0) | |
| No interpretation reported | 522 (34.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (20.0) | 1 (7.7) | 2 (3.2) | 2 (2.9) | 2 (2.4) | 3 (2.8) | 48 (22.7) | 197 (50.0) | 266 (48.2) | |
| Results pending/unknown | 113 (7.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (40.0) | 2 (15.4) | 5 (7.9) | 6 (8.6) | 7 (8.4) | 11 (10.1) | 24 (11.4) | 22 (5.6) | 34 (6.2) | |
| Percentage of cells staining for PD-L1 among those tested, no. (%)[c] | | | | | | | | | | | | | | <.001 |
| <1% | 312 (20.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (20.) | 1 (7.7) | 9 (14.3) | 11 (15.7) | 16 (19.3) | 29 (26.6) | 41 (19.4) | 64 (16.2) | 140 (25.4) | |
| 1-49% | 285 (19.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (30.8) | 14 (22.2) | 21 (30.0) | 20 (24.1) | 22 (20.2) | 27 (12.8) | 63 (16.0) | 114 (20.7) | |
| ≥50% | 622 (41.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 11 (7.7) | 18 (28.6) | 16 (22.9) | 24 (28.9) | 28 (25.7) | 92 (43.6) | 213 (54.1) | 230 (41.7) | |
| Unknown/missing | 283 (18.8) | 0 (0.0) | 0 (0.0) | 2 (100.0) | 4 (80.0) | 7 (53.8) | 22 (34.9) | 22 (31.4) | 23 (27.7) | 30 (27.5) | 51 (24.2) | 54 (13.7) | 68 (12.3) | |
| Therapy class received before PD-(L)1 inhibitor, no. (%) | | | | | | | | | | | | | | <.001 |
| ALK inhibitor | 29 (0.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.5) | 5 (0.8) | 4 (0.6) | <4 | 4 (0.8) | <4 | 4 (0.5) | 4 (0.5) | |
| Anti-VEGF-based | 992 (18.9) | 1 (100.0) | 1 (33.3) | 3 (9.7) | 16 (8.1) | 75 (17.4) | 146 (24.0) | 140 (21.3) | 122 (20.6) | 112 (21.1) | 126 (18.8) | 135 (18.0) | 115 (14.6) | |
| Clinical study drug-based | 19 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.5) | 0 (0.0) | 2 (0.3) | 6 (1.0) | 1 (0.2) | 3 (0.4) | 4 (0.5) | 1 (0.1) | |
| EGFR TKIs | 283 (5.4) | 0 (0.0) | 2 (66.7) | 4 (12.9) | 12 (6.1) | 34 (7.9) | 44 (7.2) | 31 (4.7) | 36 (6.1) | 24 (4.5) | 31 (4.6) | 33 (4.4) | 32 (4.1) | |
| EGFR-antibody based | 29 (0.6) | 0 (0.0) | 0 (0.0) | 1 (3.2) | 1 (0.5) | 1 (0.2) | 0 (0.0) | 1 (0.2) | 2 (0.3) | 5 (0.9) | 6 (0.9) | 7 (0.9) | 5 (0.6) | |
| No prior therapy received | 1329 (25.3) | 0 (0.0) | 0 (0.0) | 3 (9.7) | 34 (17.3) | 60 (13.9) | 92 (15.1) | 123 (18.8) | 119 (20.1) | 100 (18.9) | 179 (26.8) | 287 (38.3) | 332 (42.1) | |

**TABLE 1.** *Continued*

| Characteristic | Overall, N = 5257 | 2014 Q3, n = 1 | 2014 Q4, n = 3 | 2015 Q1, n = 31 | 2015 Q2, n = 197 | 2015 Q3, n = 432 | 2015 Q4, n = 608 | 2016 Q1, n = 656 | 2016 Q2, n = 592 | 2016 Q3, n = 530 | 2016 Q4, n = 669 | 2017 Q1, n = 750 | 2017 Q2, n = 788 | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nonplatinum-based chemotherapy combinations | 36 (0.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (1.0) | 8 (1.9) | 8 (1.3) | 11 (1.7) | 3 (0.5) | 2 (0.4) | 0 (0.0) | 1 (0.1) | 1 (0.1) | |
| Other therapies | 10 (0.2) | 0 (0.0) | 0 (0.0) | 2 (6.5) | 0 (0.0) | 0 (0.0) | 3 (0.5) | 1 (0.2) | 2 (0.3) | 1 (0.2) | 1 (0.1) | 0 (0.0) | 0 (0.0) | |
| Platinum-based chemotherapy combinations | 1969 (37.5) | 0 (0.0) | 0 (0.0) | 11 (35.5) | 85 (43.1) | 155 (35.9) | 209 (34.4) | 255 (38.9) | 241 (40.7) | 238 (44.9) | 270 (40.4) | 245 (32.7) | 260 (33.0) | |
| Single-agent chemotherapies | 561 (10.7) | 0 (0.0) | 0 (0.0) | 7 (22.6) | 47 (23.9) | 95 (22.0) | 101 (16.6) | 88 (13.4) | 58 (9.8) | 43 (8.1) | 50 (7.5) | 34 (4.5) | 38 (4.8) | |

Abbreviations: IQR, interquartile range; PD-(L)1, PD-1 and/or PD-L1; Q1-Q4, third through fourth quarters, respectively; TKIs, tyrosine kinase inhibitors.

[a]For additional demographic and clinical characteristics, see Supporting Table 2.

[b]This is defined as the first order or administration of nivolumab, atezolizumab, or pembrolizumab. Patients who were aged >85 years at the time of PD-(L)1 initiation were included with those aged 85 years to prevent re-identification.

[c]Biomarker status on or before starting the first PD-(L)1 inhibitor line of therapy. In cases where a patient had multiple tests for a particular biomarker, the result of the most recent successful test before the start of PD-(L)1 therapy is displayed.

[d]PD-L1 status captures the interpretation documented in the test report, which is influenced by the reference range for that specific PD-L1 test.

Patient and disease characteristics for the overall cohort and over time are shown in Table 1 and Supporting Table 2. Over the study period, the proportion of patients aged ≥75 years at the time they initiated PD-(L)1 inhibitor treatment increased (28% in Q3 2015 [n = 432] vs 34% in Q2 2017 [n = 788]), as did the proportion of patients with stage IV disease at initial diagnosis (53% in Q3 2015 vs 68% in Q2 2017). The distribution of the type and number of lines of therapy received before the earliest PD-(L)1 inhibitor-containing regimen also changed by quarter.

Biomarker testing increased throughout the study period, particularly PD-L1 testing (from 3% in Q3 2015 to 70% in Q2 2017). Over time, the proportion of patients with PD-L1 test results reported in a binary fashion (ie, interpretation of results as positive or negative, often without reporting details on the actual staining percentages) decreased in favor of PD-L1 test results reported solely as a percentage of stained cells.

The proportion of patients tested for PD-L1 before initiation of their first PD-(L)1 inhibitor increased after the initial pembrolizumab approval for advNSCLC (second-line) in October 2015 and again after the approval of first-line pembrolizumab in October 2016. This trend held overall and for each PD-L1 percentage cell staining category, with the largest increase for patients who had ≥50% of cells stained for PD-L1 (see Supporting Figs. 2 and 3, Supporting Tables 3a and 3b). Of the 1219 patients with a documented PD-L1 cell staining percentage (23%; n = 5257), 51% had ≥50% staining, and the proportion increased to 64% for those who received first-line PD-L1 inhibitor therapy (n = 632).

### *Overall and Real-World Progression-Free Survival*

For the overall cohort, the estimated median OS was 9.3 months (95% CI, 8.9-9.8 months), and the estimated median rwPFS was 3.2 months (95% CI, 3.1-3.3 months) (Fig. 2A). Median OS estimates stratified based on patient and disease characteristics are shown in Table 2. Of note, median OS ranged from 1.1 months (95% CI, 0.9-4.6 months) for patients with moderate hepatic failure at initiation of PD-(L)1 inhibitor therapy to 9.3 months (95% CI, 8.8-9.8 months) for patients with normal baseline hepatic function. For patients with and without an *EGFR* mutation, the median OS was 6.4 months (95% CI, 5.3-8.8 months) and 10.2 months (95% CI, 9.5-11.1 months), respectively. For patients with and without an *ALK* rearrangement, the median OS was 4.7 months (95% CI, 2.7 months to not reached) and 9.7 months (95% CI, 9.2-10.6 months), respectively.

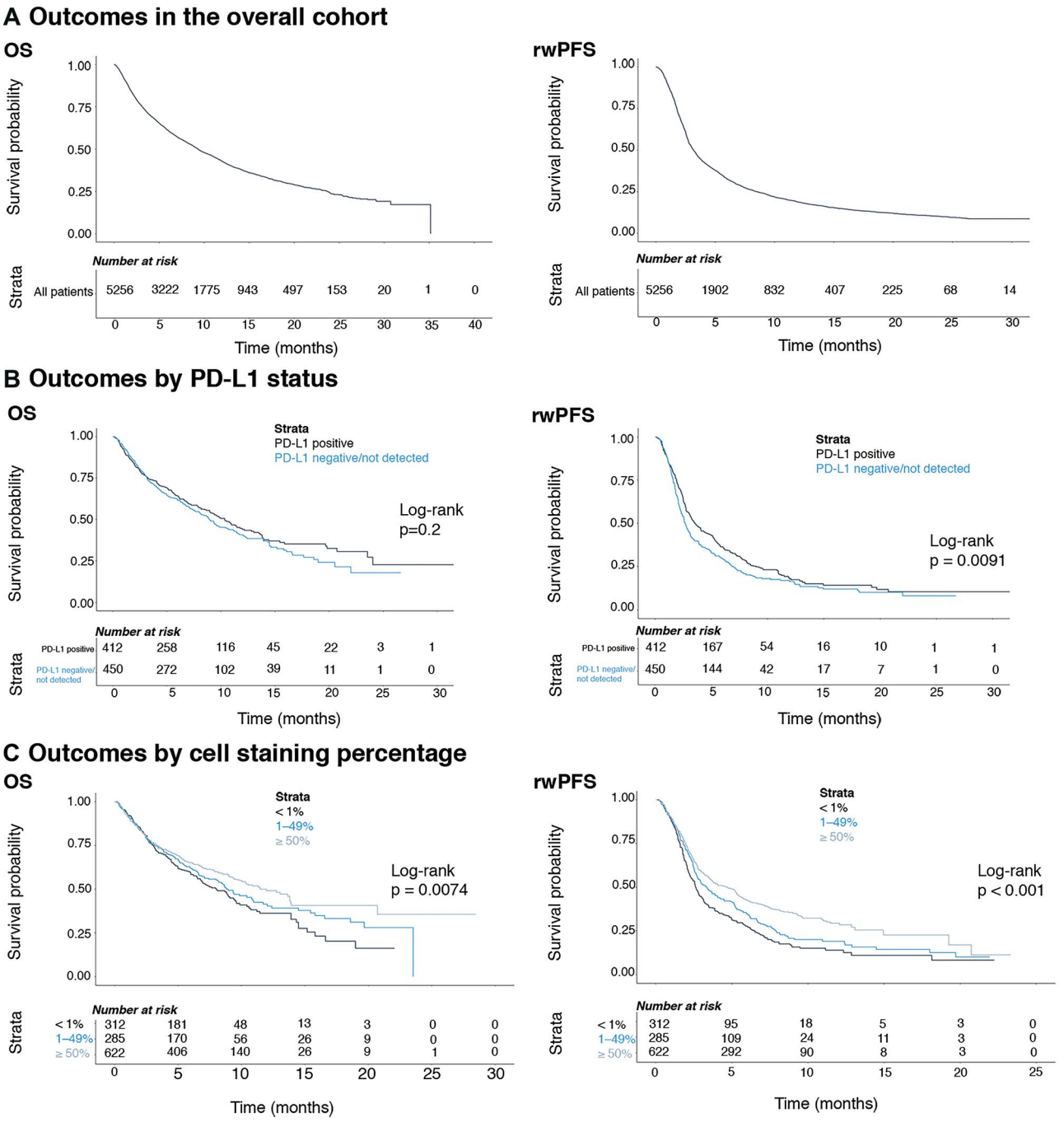


**Figure 2.** (A-C) Overall survival (OS) and real-world progression-free survival (rwPFS) are illustrated. In C, percentages (1%, 49%, and 50%) refer to the percentage of cells that stained positive for PD-L1 in a tumor sample and represent the approved staining thresholds for PD-(L)1 therapy in non–small cell lung cancer.

When a PD-(L)1 inhibitor was received in the first-line setting, the median OS was 10.8 months (95% CI, 9.6-11.7 months), compared with 8.9 months (95% CI, 7.2-10.8 months) when the first PD-(L)1 inhibitor was received in the fourth or later lines. In the subcohort of 1219 patients whose PD-L1 test report included a cell staining percentage (23%; n = 5257), median OS was 11.5, 8.8, and 8.0 months for those with ≥50%, from 1% to 49%, and <1% cell staining, respectively. In contrast, in the smaller (and not mutually exclusive) group

of 862 patients whose report provided an interpretation of PD-L1 test results (16%; n = 5257), those with results classified as positive and negative had a median OS of 10.4 and 9 months, respectively. rwPFS differed by PD-L1 cell staining level (Fig. 2C) and by stratification according to PD-(L)1 initiation date relative to pembrolizumab approval dates for advNSCLC (before/after) (see Supporting Fig. 4 and Supporting Tables 3a and 3b); as well as by the interpretation of PD-L1 status documented in the report (Fig. 2B).

Comparisons across other subgroups revealed rwPFS trends similar to those observed for OS, with the following exceptions: 1) histology and *ALK* rearrangement, in which differences between subgroups were observed for OS but not for rwPFS (although rwPFS differences approached statistical significance); and 2) median household income quartile and age at PD-(L)1 inhibitor initiation, in which differences between subgroups were observed for rwPFS but not for OS (Table 2).

### *Correlation Between Real-World Outcomes*

Among the 3157 patients who died during the study period (60%; n = 5257), the correlation between rwPFS and OS was $\rho = 0.75$ (95% CI, 0.73-0.76). Of the 1655 patients with both an rwP and a death event, the correlation between rwTTP and OS was $\rho = 0.60$ (95% CI, 0.57-0.63). Correlations between OS and treatment-based endpoints also varied. Among the 856 patients with both a death event and treatment subsequent to the index PD-(L)1 inhibitor-containing treatment regimen (16%), the correlation between OS and rwTTNT was $\rho = 0.60$ (95% CI, 0.56-0.64). The correlation between OS and rwTTD for patients with a death event (60%) was $\rho = 0.81$ (95% CI, 0.80-0.82).

## DISCUSSION

This retrospective study analyzed outcomes in a large, longitudinal cohort of real-world patients with advNSCLC who received treatment with PD-(L)1 inhibitors before July 1, 2017. This study expands our prior description[4] of early real-world use of PD-(L)1 inhibitors among patients with metastatic NSCLC and survival (cohort size nearly quadrupled, and observation time doubled), and it adds assessments of real-world intermediate endpoints (rwPFS, rwTTP, rwTTNT, and rwTTD).

Over the study period, overall PD-(L)1 inhibitor use increased and shifted toward earlier lines, concurrent with an increase in the proportion of patients tested for PD-L1 expression before PD-(L)1 inhibitor initiation. These trends demonstrate dramatic changes in real-world advNSCLC treatment and testing patterns after drug approvals and emerging evidence about the implications of PD-L1 expression levels.

Median OS and rwPFS were longer for first-line PD-(L)1 inhibitor treatment compared with later lines (and were similar across all subsequent lines). In our previous report, OS for patients with metastatic NSCLC who were treated with a PD-1 inhibitor appeared to be unaffected by therapy line.[4] Although differences in index dates prevent direct comparison, this shift likely reflects maturation in the clinical use and understanding of PD-(L)1 inhibitors. For example, patients treated with pembrolizumab were better represented in the current analysis than in the prior report. The original approval indication for pembrolizumab as front-line therapy was restricted to patients with high PD-L1 expression. Therefore, the differential toward greater benefit in first-line therapy may have been driven by the enrichment from patients who had PD-L1 staining >50%, relative to our prior report.

We consider the results of traditionally designed PD-(L)1 inhibitor clinical trials important reference points, although cohort differences prevent direct cross-study comparisons (Table 3).[5,8-11,18] Typically, real-world patients fare worse than those in clinical trials; this may reflect the more heterogeneous characteristics and differences in protocol-specified trial procedures versus real-world treatment patterns.[7] As would be expected from a real-world cohort, some of the characteristics of our population were different from clinical trials in this setting: these patients had higher rates of organ dysfunction, older age, and were more racially diverse. Yet outcomes in this study were similar or only slightly worse than those in the clinical trials that evaluated these drugs as monotherapy and were similar across cohort age groups. The relative tolerability of PD-(L)1 inhibitor treatment and optimization of its management over time may have helped close the gap between real-world effectiveness and trial efficacy.

The estimated median rwPFS in this cohort was similar to that observed in all pivotal PD-(L)1 inhibitor trials, except for 1 trial that was restricted to patients without an *EGFR* mutation or *ALK* rearrangement. PFS concordance between real-world patients and traditional clinical trial cohorts has also been observed before.[19] rwPFS, an intermediate endpoint, may be linked more closely to treatment effect than to OS, because OS inherently captures the impact of all subsequent therapies administered to the patient after the PD-(L)1 inhibitor-containing regimen.

**TABLE 2.** Overall and Real-World Progression-Free Survival by Subgroups of Interest According to Demographic Patient Characteristics

| Characteristic | OS | | | | | rwPFS | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of Patients | No. of Events (%) | Median OS, mo | 95% CI | Log-Rank *P* | No. of Events (%) | Median rwPFS, mo | 95% CI | Log-Rank *P* |
| Age categories at PD-(L)1 inhibitor initiation, y[a] | | | | | | | | | |
| ≤49 | 160 | 92 (57.5) | 9.11 | 6.26-12.26 | | 125 (78.1) | 2.49 | 2.07-3.21 | |
| 50-64 | 1584 | 940 (59.3) | 9.34 | 8.2-10.46 | .204 | 1287 (81.2) | 2.85 | 2.72-3.02 | .035 |
| 65-74 | 1930 | 1160 (60.1) | 9.74 | 8.98-10.89 | | 1572 (81.5) | 3.25 | 2.98-3.48 | |
| ≥75 | 1582 | 965 (61.0) | 8.98 | 8.33-9.57 | | 1258 (79.5) | 3.51 | 3.34-3.87 | |
| Sex | | | | | | | | | |
| Male | 2819 | 1750 (62.1) | 8.79 | 8.16-9.38 | <.001 | 2309 (81.9) | 2.95 | 2.79-3.11 | <.001 |
| Female | 2437 | 1407 (57.7) | 9.84 | 9.31-10.85 | | 1933 (79.3) | 3.41 | 3.25-3.64 | |
| Smoking status | | | | | | | | | |
| History of smoking | 4679 | 2796 (59.8) | 9.41 | 9.05-10.1 | .019 | 3743 (80.0) | 3.31 | 3.15-3.44 | <.001 |
| No history of smoking | 553 | 343 (62.0) | 8.49 | 7.11-9.57 | | 479 (86.6) | 2.56 | 2.39-2.82 | |
| Median household income, zip-code level | | | | | | | | | |
| 1: Lowest | 719 | 414 (57.6) | 9.64 | 7.61-11.51 | | 558 (77.6) | 3.48 | 3.02-3.93 | |
| 2 | 1121 | 654 (58.3) | 10.03 | 9.15-11.9 | .176 | 867 (77.3) | 3.51 | 3.21-3.9 | .001 |
| 3 | 1317 | 827 (62.8) | 9.15 | 8.23-10.16 | | 1087 (82.5) | 3.08 | 2.89-3.31 | |
| 4: Highest | 2058 | 1236 (60.1) | 9.08 | 8.62-9.61 | | 1700 (82.6) | 3.05 | 2.89-3.25 | |
| Race/ethnicity | | | | | | | | | |
| White | 3685 | 2247 (61.0) | 9.31 | 8.85-9.93 | | 3004 (81.5) | 3.18 | 3.02-3.34 | |
| Black or African American | 445 | 247 (55.5) | 10.98 | 9.05-12.33 | .193 | 334 (75.1) | 3.18 | 2.75-3.8 | .176 |
| Asian | 131 | 65 (49.6) | 11.97 | 10.26-14.89 | | 106 (80.9) | 3.05 | 2.39-4.13 | |
| Other | 505 | 301 (59.6) | 8.95 | 7.87-10.36 | | 403 (79.8) | 3.21 | 2.89-3.61 | |
| Region of residence | | | | | | | | | |
| Midwest | 1150 | 734 (63.8) | 9.21 | 8.43-10.13 | | 938 (81.6) | 3.41 | 3.11-3.7 | |
| Northeast | 1308 | 809 (61.9) | 8.95 | 7.84-10.1 | .052 | 1075 (82.2) | 2.95 | 2.75-3.18 | .167 |
| South | 1981 | 1170 (59.1) | 9.15 | 8.49-9.87 | | 1587 (80.1) | 3.21 | 3.02-3.44 | |
| West | 750 | 415 (55.3) | 10.59 | 9.08-11.8 | | 597 (79.6) | 3.25 | 2.92-3.51 | |
| Patient clinical characteristics | | | | | | | | | |
| Group stage at initial diagnosis | | | | | | | | | |
| Stage 0/I | 386 | 214 (55.4) | 10.92 | 9.34-13.54 | | 298 (77.2) | 3.90 | 3.41 5.31 | |
| Stage II | 338 | 188 (55.6) | 11.97 | 10.49-13.64 | <.001 | 274 (81.1) | 3.77 | 3.25-4.82 | <.001 |
| Stage III | 1216 | 733 (60.3) | 10.10 | 9.38-11.44 | | 958 (78.8) | 3.44 | 3.21-3.80 | |
| Stage IV | 3159 | 1931 (61.1) | 8.30 | 7.77-8.95 | | 2584 (81.8) | 2.89 | 2.75-3.05 | |
| Histology | | | | | | | | | |
| Nonsquamous cell carcinoma | 3510 | 2010 (57.3) | 9.87 | 9.28-10.79 | .001 | 2801 (79.8) | 3.18 | 3.05-3.38 | .459 |
| Squamous cell carcinoma | 1535 | 1005 (65.5) | 8.95 | 8.03-9.61 | | 1274 (83.0) | 3.21 | 2.95-3.48 | |
| Renal function when patient initiated PD-(L)1[b] | | | | | | | | | |
| Normal renal function | 3997 | 2431 (60.8) | 9.05 | 8.66-9.48 | | 3261 (81.6) | 3.02 | 2.92-3.18 | |
| Moderate renal failure | 97 | 63 (64.9) | 10.26 | 7.34-13.57 | .777 | 81 (83.5) | 3.20 | 2.72-4.82 | .846 |
| Severe renal failure | 19 | 12 (63.2) | 8.30 | 1.93, NA | | 13 (68.4) | 2.69 | 1.38, NA | |
| Hepatic function when patient initiated PD-(L)1[c] | | | | | | | | | |
| Normal hepatic function | 3825 | 2312 (60.4) | 9.31 | 8.82-9.77 | | 3121 (81.6) | 3.02 | 2.92-3.18 | |
| Moderate hepatic failure | 34 | 29 (85.3) | 1.15 | 0.89-4.59 | <.001 | 30 (88.2) | 1.15 | 0.89-2.66 | <.001 |
| Severe hepatic failure | 16 | 12 (75.0) | 1.39 | 0.36, NA | | 15 (93.8) | 1.33 | 0.36-4.00 | |

**TABLE 2.** *Continued*

| Characteristic | OS | | | | | rwPFS | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of Patients | No. of Events (%) | Median OS, mo | 95% CI | Log-Rank *P* | No. of Events (%) | Median rwPFS, mo | 95% CI | Log-Rank *P* |
| Patient biomarker status | | | | | | | | | |
| PD-L1 expression status among those tested[d,e] | | | | | | | | | |
| PD-L1–positive | 412 | 211 (51.2) | 10.36 | 8.95-12.16 | .2 | 311 (75.5) | 3.54 | 3.08-4.43 | .009 |
| PD-L1–negative/not detected | 450 | 246 (54.7) | 8.95 | 7.97-10.59 | | 365 (81.1) | 2.66 | 2.46-3.02 | |
| Percentage of cells staining for PD-L1[d] | | | | | | | | | |
| <1% | 312 | 171 (54.8) | 8.03 | 6.79-9.57 | | 255 (81.7) | 2.62 | 2.33-3.02 | |
| 1%-49% | 285 | 144 (50.5) | 8.82 | 7.41-11.70 | .007 | 213 (74.7) | 3.34 | 2.72-4.20 | <.001 |
| ≥50% | 622 | 270 (43.4) | 11.48 | 10.33-13.87 | | 402 (64.6) | 4.69 | 3.7-5.34 | |
| *ALK* status among those tested[d] | | | | | | | | | |
| Rearrangement present | 45 | 30 (66.7) | 4.66 | 2.72, NA | .038 | 39 (86.7) | 1.97 | 1.48-3.41 | .05 |
| Rearrangement not present | 3099 | 1792 (57.8) | 9.7 | 9.18-10.59 | | 2480 (80.0) | 3.18 | 2.98-3.34 | |
| *EGFR* status among those tested[d] | | | | | | | | | |
| Mutation positive | 253 | 163 (64.4) | 6.43 | 5.28-8.79 | .001 | 228 (90.1) | 2.20 | 2.03-2.56 | <.001 |
| Mutation negative | 3109 | 1779 (57.2) | 10.20 | 9.48-11.08 | | 2467 (79.4) | 3.34 | 3.15-3.48 | |
| PD-(L)1 inhibitor line of therapy | | | | | | | | | |
| Line no. of first PD-(L)1 inhibitor in advanced setting | | | | | | | | | |
| 1 | 1329 | 696 (52.4) | 10.75 | 9.61-11.7 | .013 | 951 (71.6) | 4.26 | 3.8-4.79 | <.001 |
| 2 | 2681 | 1652 (61.6) | 8.75 | 8.20-9.31 | | 2216 (82.7) | 2.98 | 2.82-3.18 | |
| 3 | 833 | 532 (63.9) | 9.38 | 7.93-10.72 | | 719 (86.3) | 2.98 | 2.62-3.21 | |
| ≥4 | 413 | 277 (67.1) | 8.85 | 7.21-10.79 | | 356 (86.2) | 2.79 | 2.56-3.02 | |
| Year and quarter (Q) in which start date of PD-(L)1 line of therapy occurred | | | | | | | | | |
| 2014 Q3 | 1 | 1 (100.0) | 9.38 | NA, NA | .049 | 1 (100.0) | 5.44 | NA, NA | <.001 |
| 2014 Q4 | 3 | 3 (100.0) | 23.70 | 15.44, NA | | 3 (100.0) | 3.90 | 1.64, NA | |
| 2015 Q1 | 31 | 25 (80.6) | 6.03 | 4.39-17.11 | | 28 (90.3) | 3.90 | 2.07-6.03 | |
| 2015 Q2 | 197 | 150 (76.1) | 7.57 | 6.07-10.26 | | 174 (88.3) | 3.34 | 2.79-4.16 | |
| 2015 Q3 | 432 | 338 (78.2) | 8.82 | 6.56-9.9 | | 400 (92.6) | 2.69 | 2.39-2.98 | |
| 2015 Q4 | 608 | 429 (70.6) | 9.31 | 7.77-10.92 | | 531 (87.3) | 2.75 | 2.62-2.98 | |
| 2016 Q1 | 655 | 434 (66.3) | 9.44 | 8.49-11.44 | | 560 (85.5) | 3.38 | 3.08-3.77 | |
| 2016 Q2 | 592 | 371 (62.7) | 11.70 | 9.7-13.25 | | 502 (84.8) | 3.44 | 3.05-3.93 | |
| 2016 Q3 | 530 | 345 (65.1) | 8.23 | 6.62-9.41 | | 448 (84.5) | 2.85 | 2.69-3.31 | |
| 2016 Q4 | 669 | 393 (58.7) | 8.69 | 7.44-10.13 | | 547 (81.8) | 3.08 | 2.75-3.57 | |
| 2017 Q1 | 750 | 358 (47.7) | 9.57 | 8.85-11.31 | | 540 (72.0) | 3.38 | 2.98-3.8 | |
| 2017 Q2 | 788 | 310 (39.3) | 8.66 | 7.9, NA | | 508 (64.5) | 3.70 | 3.31-4.59 | |
| Therapy class received prior to PD-(L)1 | | | | | | | | | |
| ALK inhibitors | 29 | 22 (75.9) | 3.51 | 2.16-8.23 | <.001 | 27 (93.1) | 1.90 | 1.28-2.98 | <.001 |
| Anti-VEGF-based | 992 | 608 (61.3) | 8.39 | 7.44-9.41 | | 840 (84.7) | 2.92 | 2.72-3.15 | |
| Clinical study drug-based | 19 | 9 (47.4) | 14.07 | 11.15, NA | | 13 (68.4) | 2.62 | 1.84, NA | |
| EGFR TKIs | 283 | 188 (66.4) | 7.61 | 6.13-10.49 | | 254 (89.8) | 2.56 | 2.23-2.98 | |
| EGFR-antibody based | 29 | 19 (65.5) | 7.84 | 2.85, NA | | 22 (75.9) | 4.26 | 2.85-7.11 | |
| No prior therapy received | 1329 | 696 (52.4) | 10.75 | 9.61-11.7 | | 951 (71.6) | 4.26 | 3.8-.79 | |
| Nonplatinum chemotherapy combinations | 36 | 22 (61.1) | 11.93 | 8.82, NA | | 28 (77.8) | 3.48 | 2.39-10.26 | |
| Other therapies | 10 | 6 (60.0) | 5.87 | 3.28, NA | | 8 (80.0) | 2.43 | 0.69, NA | |
| Platinum-based chemotherapy combinations | 1968 | 1231 (62.6) | 8.98 | 8.26-9.51 | | 1628 (82.7) | 2.92 | 2.79-3.11 | |
| Single-agent chemotherapies | 561 | 356 (63.5) | 11.18 | 9.18-12.52 | | 471 (84.0) | 3.38 | 3.02-3.9 | |

**TABLE 2.** *Continued*

| Characteristic | OS | | | | | rwPFS | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of Patients | No. of Events (%) | Median OS, mo | 95% CI | Log-Rank *P* | No. of Events (%) | Median rwPFS, mo | 95% CI | Log-Rank *P* |
| No. of patients on a PD-(L)1 inhibitor by site[f] | | | | | | | | | |
| 1 | 1759 | 1031 (58.6) | 9.28 | 8.56-10.16 | | 1410 (80.2) | 3.31 | 3.05-3.48 | |
| 2 | 1814 | 1083 (59.7) | 9.61 | 8.95-10.82 | .708 | 1473 (81.2) | 3.08 | 2.85-3.25 | .359 |
| 3 | 1683 | 1043 (62.0) | 9.08 | 8.20-9.84 | | 1359 (80.7) | 3.21 | 2.98-3.44 | |

Abbreviations: NA, not available; PD-(L)1, PD-1 and/or PD-L1; TKIs, tyrosine kinase inhibitors.
[a]This is defined as age at the first order or administration of nivolumab, atezolizumab, or pembrolizumab. Patients who were aged >85 years at the time of PD-(L)1 initiation were included with those aged 85 years to prevent re-identification.
[b]Renal function classification followed Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, in which serum creatinine is considered normal when it is <1.5 times the upper limit of the normal range. The analysis was restricted to patients who had results up to 30 days before the index date.
[c]Liver function classification was determined by serum bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (ALT) classification. Normal liver function was defined as normal values for all 3 laboratory tests as classified by CTCAE version 5.0: normal bilirubin is <1.5 times the upper limit of the normal range, and normal AST and ALT values are <3.0 times the upper limit of the normal range. The analysis was restricted to patients who had results for all 3 laboratory tests up to 30 days before the index date.
[d]Biomarker status is indicated on or before the first PD-(L)1 inhibitor line of therapy started. For patients who had multiple tests for a particular biomarker, the result of the most recent successful test before the start of PD-(L)1 therapy is displayed.
[e]PD-L1 status captures the interpretation provided in the test report, which is influenced by the reference range for that specific PD-L1 test.
[f]Site stratification refers to "practice sites" defined by tax identification number.

**TABLE 3.** Outcomes From the Current Real-World Cohort and From Randomized Controlled Trials of Nivolumab, Pembrolizumab, and Atezolizumab Monotherapy That Were Reported During the Study Period[a]

| Description | No. | Median OS (95% CI), mo | Median PFS or rwPFS (95% CI), mo |
|---|---|---|---|
| Nivolumab 2L | | | |
| Squamous | 272 | 9.2 (7.3-13.3) | 3.5 |
| Nonsquamous | 292 | 12.2 (9.7-15.0) | 2.3 |
| Pembrolizumab 2L | | | |
| All patients | 313 | 12.0 (9.3-14.7) | 3.7 (2.9-4.1) |
| Previously treated patients only | 233 | 9.3 (8.4-12.4) | 3.0 (2.2-4.0) |
| Pembrolizumab 1L | | | |
| No EGFR+/ALK+ | | Not reported yet | 10.3 (6.7 to not reached) |
| Atezolizumab 2L | | | |
| All patients | 425 | 13.8 (11.8-15.7) | NA |
| Squamous | 112 | 8.9 (7.4-12.8) | NA |
| Nonsquamous | 313 | 15.6 (13.3-17.6) | NA |
| PD-L1 >1% | 241 | 15.7 (12.6-18.0) | NA |
| Current cohort | | | |
| All patients | 5258 | 9.3 (8.9-9.8) | 3.18 (3.1-3.3) |
| Squamous | 1005 | 8.9 (8.0-9.6) | 3.2 (3.0-3.5) |
| Nonsquamous | 3511 | 9.9 (9.3-10.8) | 3.2 (3.05-3.4) |
| PD-L1 "positive" | 412 | 10.4 (9.0-12.2) | 3.5 (3.1-4.4) |
| ≥50% Cell staining in PD-L1 test | 622 | 11.5 (10.3-13.9) | 4.7 (3.7-5.3) |

Abbreviations: +, positive; 1L, first line; 2L, second line; NA, not applicable; OS, overall survival; PFS, progression-free survival; rwPFS, real-world progression-free survival.
[a]This side-by-side summary of results from the current study with available traditional clinical trial results is provided as a high-level benchmark. Direct comparisons are not possible because of differences in the populations studied.[5,8-11,18]

The stronger correlation between OS and rwTTD compared with OS and rwPFS differs from typical cytotoxic therapy findings.[20] This could reflect the practice of treatment beyond RECIST-defined progression, because OS and rwTTD capture the benefit of the additional immunotherapy exposure, but rwPFS does not; further research is ongoing. The lowest correlations with OS were observed for rwTTNT and rwTTP. In addition to the effect of treatment past RECIST-defined progression, the exclusion of death as an rwTTP event can weaken the relationship with OS in a short survival setting. For rwTTNT, its correlation with OS may reflect a durable survival benefit even for those who discontinue immunotherapy early because of immune-mediated toxicity or other nonprogression-related reason.[21] These intermediate endpoint findings could be helpful to clinicians and patients because they reflect real-world treatment patterns and outcomes; however, in this real-world cohort, as in clinical trials, their overall association with OS was low to moderate.[22-28]

Similar to prior traditional clinical trials and retrospective research,[4] outcomes were worse for men,

nonsmokers, and patients with *EGFR* mutations or *ALK* rearrangements. This subgroup consistency offers an additional external validation datapoint for clinical trial findings. Median OS and rwPFS for patients with renal dysfunction at baseline were similar, but those with moderate or severe hepatic failure at the initiation of PD-(L)1 inhibitor therapy had noticeably worse outcomes. Because monoclonal antibodies are not metabolized in the liver, this finding may reflect a larger hepatic tumor burden, which may be associated with more advanced disease and decreased survival. Analyses of large, contemporary RWD sources may be the earliest (and sometimes the only) mechanism with which to evaluate these subgroups, which often are excluded from traditional clinical trials.

This longitudinal real-world cohort also revealed OS differences based on immunohistochemical PD-L1 staining reported as the percentage of stained cells, but not for binary positive/negative report interpretations (a smaller, nonmutually exclusive group). This observation may be a signal of how the clinical shift toward a more nuanced understanding of PD-L1 results and management of immunotherapy in general, such as treating past RECIST-based progression, may have a favorable impact on outcomes. As the output from the active research on the predictive value of PD-L1 expression,[5,18,29] and other potential improvements in the clinical use of immunotherapy, is assimilated across health care delivery systems, including providers, administrators, and/or payors, future studies will further explore the impact of these developments.

The similarity in OS between the PD-L1–positive and PD-L1–negative groups (based on reported interpretation) in this cohort contrasts with findings from the prior report in the first year after approval.[4] Several trends at work in the period between both analyses may have contributed to this finding. The shift toward first-line use over time may have ushered in a shift in the characteristics of patients treated with PD-(L)1 inhibitors. PD-L1 expression testing and reporting practices also evolved: 1) testing rates before the initiation of PD-(L)1 inhibitor treatment increased; 2) the proportion of PD-L1 reports with a binary positive/negative result interpretation started decreasing in Q4 2016, and the concomitant increase in reports without a binary result interpretation may have coincided with the progressive optimization of immunotherapy use; and 3) patients with PD-L1 negative reports were over-represented in the positive/negative interpretation group in later months of the study period (Table 1).[30,31] When interpreting PD-L1 test reports, clinicians need to be aware that not all reports (especially older ones) document percentage staining results and that underlying thresholds for PD-L1 positivity may have varied. This evolution in reporting and documentation practices (eg, positive/negative and/or percentage staining) highlights the importance of carefully defined RWD variables that are harmonized and normalized. Standardized data models, endpoint definitions, and analytic approaches are needed for reliable and clinically meaningful outcome comparisons over time and across data sets.

A limitation of this study is that EHRs, the data source, are optimized not for research but, rather, for clinical documentation, practice management, and billing. To create a research-quality data set, we applied strict rules to extract clinically relevant data and implemented quality-control procedures to maximize data integrity. Lines of therapy were defined using a rule-based algorithm. Therefore, accuracy depends on complete treatment documentation. For other variables, we also relied on EHR content, which often lacked Eastern Cooperative Oncology Group performance status data and may have had incomplete information about comorbidities and biomarker testing status; more generally, practical factors, such as clinic work-flow practices impacting documentation of reports into EHRs, patients exiting their care system, or unspecified loss to follow-up, all may contribute to a degree of incompleteness in our source data. These types of missing data may introduce bias; for example, patients who return to their home country may have missing date of death information that could lead to a minor overestimation of survival. Date of death was based on a high-sensitivity composite mortality data set that yields OS data close to that of the National Death Index; although it is the current US gold standard, the National Death Index has limited refresh frequency (annual) and has a 2-year reporting delay.[16]

This study of a large, contemporary, real-world cohort patients with advNSCLC who received treatment with PD-(L)1 inhibitors identified clinically relevant findings that may aid decision making: 1) PD-(L)1 inhibitor treatment moved from later line into first-line over a short time period; 2) correlation between OS and rwTTD was stronger compared with OS and rwPFS; 2) liver dysfunction was associated with decreased OS, whereas renal dysfunction was not; and 3) OS and rwPFS were associated with PD-L1 percentage staining results, but only rwPFS was associated with positive/negative status classification. Variations in real-world

reporting of PD-L1 test results and interpretations should be considered in practice. As PD-L1 expression testing becomes increasingly granular and more novel outcome predictors emerge, EHR-derived RWD will be a key evidence source in this rapidly evolving field, possibly helping define the real-world prognostic and/or predictive value of PD-L1 test results. Studying the currently shifting immunotherapy landscape is only possible with a large, contemporary, and detailed longitudinal real-world data set. In addition, evaluation of a full set of intermediate endpoints (rwPFS, rwTTD, rwTTNT, rwTTP) and their relationships with OS as part of a standard portfolio of real-world endpoints will enable the most clinically meaningful assessment of real-world outcomes and facilitate decision-making.

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## CONFLICT OF INTEREST DISCLOSURES

Rebecca A. Miksad, Johan Adami, Mariel Boyd, Nicholas R. Brown, Anala Gossai, Irene Kaganman, Deborah Kuk, Jillian M. Rockland, Aracelis Z. Torres, and Amy P. Abernethy were employed at Flatiron Health, Inc, at the time of this study and report equity ownership in Flatiron Health. Rebecca A. Miksad, Johan Adami, Mariel Boyd, Nicholas R. Brown, Anala Gossai, Deborah Kuk, Jillian M. Rockland, Aracelis Z. Torres, and Amy P. Abernethy report stock ownership in Roche. Rebecca A. Miksad reports personal fees from the De Luca Foundation. Irene Kaganman reports employment at Bristol-Myers Squibb. At the time of this work, Amy P. Abernethy was chief medical, chief scientific officer, and senior vice president of oncology at Flatiron Health, Inc. which is an independent subsidiary of the Roche Group, and had stock ownership in Roche. At that time, she also declared the following: serving on the board of directors and stock ownership of Athenahealth and CareDx; owner of Orange Leaf Associates, LLC; senior advisor of Highlander Partners; advisor of SignalPath Research, RobinCare, and KelaHealth, Inc.; special advisor of The One Health Company; receiving honoraria from Roche/Genentech (<USD$10K per year); and having a patent pending for a technology that facilitates the extraction of unstructured information from medical records. All of these relationships ended on or before 1/31/2019, predating her joining the US Food and Drug Administration (FDA), except for Orange Leaf Associates, LLC. Since joining FDA, Amy P. Abernethy has complied with applicable ethics laws. Sean Khozin, Richard Pazdur, and Jizu Zhi made no disclosures.

## AUTHOR CONTRIBUTIONS

Conception and design of this article: **Sean Khozin**, **Rebecca A. Miksad**, **Anala Gossai**, **Deborah Kuk**, **Aracelis Z. Torres**, **Richard Pazdur**, **Jizu Zhi**, and **Amy P. Abernethy**. Providing study material or patients: **Johan Adami**, **Mariel Boyd**, **Jillian M. Rockland**. Collecting and/or assembling data: **Rebecca A. Miksad**, **Johan Adami**, **Mariel Boyd**, **Jillian M. Rockland**. All authors participated in data analysis and interpretation, writing the article, and approved the final version.

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