Title

First-Line Systemic Treatments for Stage IV Non-Small Cell Lung Cancer in California: Patterns of Care and Outcomes in a Real-World Setting.

Journal

JNCI Cancer Spectrum, 3(3)

Authors

Maguire, Frances

Morris, Cyllene

Parikh-Patel, Arti

et al.

Publication Date

2019-09-01

DOI

10.1093/jncics/pkz020

Peer reviewed

JNCI Cancer Spectrum (2019) 3(3): pkz020

doi: 10.1093/jncics/pkz020
First published online April 4, 2019
Article

ARTICLE

First-Line Systemic Treatments for Stage IV Non-Small Cell Lung Cancer in California: Patterns of Care and Outcomes in a Real-World Setting

Frances B. Maguire, Cyllene R. Morris, Arti Parikh-Patel, Rosemary D. Cress, Theresa H. M. Keegan, Chin-Shang Li, Patrick S. Lin, Kenneth W. Kizer

See the Notes section for the full list of authors' affiliations.
Correspondence to: Frances B. Maguire, PhD, MPH, California Cancer Reporting and Epidemiologic Surveillance Program, University of California Davis Health, 1631 Alhambra Blvd., Suite 200, Sacramento, CA 95816 (e-mail: fbmaguire@ucdavis.edu).

Abstract

Background: Multiple systemic treatments have been developed for stage IV non-small cell lung cancer (NSCLC), but their use and effect on outcomes at the population level are unknown. This study describes the utilization of first-line systemic treatments among stage IV NSCLC patients in California and compares survival among treatment groups.
Methods: Data on 17 254 patients diagnosed with stage IV NSCLC from 2012 to 2014 were obtained from the California Cancer Registry. Systemic treatments were classified into six groups. The Kaplan-Meier method and multivariable Cox proportional hazards models were used to compare survival between treatment groups.
Results: Fifty-one percent of patients were known to have received systemic treatment. For patients with nonsquamous histology, pemetrexed regimens were the most common treatment (14.8%) followed by tyrosine kinase inhibitors (11.9%) and platinum doublets (11.5%). Few patients received pemetrexed/bevacizumab combinations (4.5%), bevacizumab combinations (3.6%), or single agents (1.7%). There was statistically significantly better overall survival for those on pemetrexed regimens (hazard ratio [HR] = 0.86, 95% confidence interval [CI] = 0.80 to 0.92), bevacizumab regimens (HR = 0.73, 95% CI = 0.65 to 0.81), pemetrexed/bevacizumab regimens (HR = 0.68, 95% CI = 0.61 to 0.76), or tyrosine kinase inhibitors (HR = 0.62, 95% CI = 0.57 to 0.67) compared with platinum doublets. The odds of receiving most systemic treatments decreased with decreasing socioeconomic status. For patients with squamous histology, platinum doublets were predominant (33.7%) and were not found to have statistically significantly different overall survival from single agents.
Conclusions: These population-level findings indicate low utilization of systemic treatments, survival differences between treatment groups, and evident treatment disparities by socioeconomic status.

Lung cancer is the second-most common cancer and the leading cancer-related cause of death in both men and women (1). Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, comprising approximately 84% of all lung cancers (2). There are two subtypes, nonsquamous and squamous. Approximately one-half (55%) of patients with NSCLC are diagnosed with distant stage disease with very poor survival rates (5% survival at 5 years) (2). Systemic therapies are the main treatment for patients with stage IV disease (3).

Many different drugs and combinations of drugs are used as first-line systemic treatment for stage IV nonsquamous NSCLC. Platinum-based chemotherapy has been used for many years and remains the mainstay of treatment (4,5). However, in the past two decades, multiple targeted drugs have been developed and used to treat stage IV nonsquamous NSCLC (6). The National Comprehensive Cancer Network (NCCN) guidelines have recommended molecular testing since 2011 to identify driver mutations for targeted therapy (7–11). A targeted agent is

Received: September 5, 2018; **Revised:** December 3, 2018; **Accepted:** March 19, 2019

recommended as first-line treatment if an actionable mutation is present. If no mutation is present, other treatment options for nonsquamous NSCLC include platinum-based chemotherapy, with or without bevacizumab (a vascular endothelial growth factor inhibitor), and/or pemetrexed (3). First-line treatment with the immune checkpoint inhibitor pembrolizumab is now also an option (12,13). For patients with poor performance status and no actionable mutations, single agents or best supportive care are recommended. If the tumor is of squamous histology, then platinum-based chemotherapy is recommended (3).

Systemic treatments, including targeted therapies, have been shown to increase survival in clinical trials (14–20). However, the administration and effectiveness of different drug combinations at the population level are unknown. Prior studies have focused on particular drug regimens, certain hospital types, small population cohorts, or non-US communities (21–27). There is a paucity of information on US population-level utilization of systemic treatments in NSCLC. This retrospective study sought to determine the use of first-line systemic treatments and compare overall survival (OS) by treatment groups among all stage IV NSCLC patients in the large and diverse California population.

Methods

Study Population

We identified patients diagnosed with a first primary, stage IV NSCLC from 2012 to 2014 who were age 20 years or older at diagnosis through the California Cancer Registry (CCR). The state-mandated CCR is a population-based cancer surveillance system that collects reports on all incident cancers diagnosed annually in California. The CCR has collected data on tumor characteristics, treatment, and patient demographics since 1988, with annual follow-up for vital status. Data are collected through a network of regional registries, which are also affiliated with the National Cancer Institute (NCI)'s Surveillance, Epidemiology, and End Results program (28–31).

Individual NSCLC patients were selected using the International Classification of Diseases for Oncology, 3rd edition, World Health Organization (ICD-O-3/WHO) site recode 2008 definition and the 2015 WHO classification of lung tumors (32,33). Included in the analysis were squamous cell carcinoma (ICD-O-3 codes: 8070, 8071, 8072, 8073, 8083, 8084, 8052, 8123), adenocarcinoma (ICD-O-3 codes: 8140, 8250, 8551, 8260, 8265, 8230, 8253, 8254, 8480, 8333, 8144, 8256, 8257, 8550, 8255, 8251, 8252, 8470, 8481, 8490), and non-small cell carcinoma not otherwise specified (NOS) (ICD-O-3 codes: 8012, 8560, 8022, 8032, 8031, 8980, 8972, 8033, 8046, 8310, 8014, 8082, 8200, 8430) (Supplementary Figure A1, available online). Stage at diagnosis was assigned using the American Joint Committee on Cancer staging system rules.

This study received an exempt determination from the University of California, Davis Institutional Review Board.

Baseline Covariates

Patient characteristics collected in the CCR and used in the analysis include sex, race/ethnicity, neighborhood socioeconomic status (SES), health insurance type, rural/urban residence, age at diagnosis, comorbidity score, treatment at NCI-designated cancer centers, tumor histology, and radiation treatment. Sex was defined as male or female. Race/ethnicity was classified as non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, and other/unknown based on the North American Association of Central Cancer Registries' Hispanic and Asian/Pacific Islander Identification Algorithm (34).

Neighborhood SES was measured using an established aggregate measure based on 2010 census block values of education, occupation, unemployment, household income, poverty, rent, and home price (35). Rural/urban residence was based on Medical Service Study Area designations and on the 2010 US Census.

Health insurance was categorized as private/military (managed care, private fee for service, health maintenance organization, preferred provider organization, Medicare with supplement NOS, Medicare with private supplement, Veterans Affairs, Tricare, military treatment facilities, insurance NOS), Medicare (Medicare through managed care plan), Medicaid/public (Medicaid, Medicaid/managed care, Medicare with Medicaid eligibility, Medicare/Medicaid NOS, county funded NOS, Indian/Public Health Service, not insured, not insured/self-pay), and unknown. Not insured was included in the Medicaid/public category because frequently uninsured cancer patients retroactively enroll in Medicaid (36).

The Charlson comorbidity index, described by Deyo et al. (37), was used to assign patient comorbidity scores of 0, 1, and 2 or more, based on 16 medical conditions, excluding cancer diagnoses, reported in the Office of Statewide Health Planning and Development patient hospital discharge data linked to the CCR database (38). Treatment at NCI-designated cancer centers was determined by reviewing all reporting facilities where a patient was treated.

Radiation treatment (yes/no) was included in the analysis because studies indicate that it may act synergistically with systemic treatments to upregulate the immune system and extend survival (39–41).

First-Line Systemic Treatment Groups

First-line systemic treatment was the primary exposure of interest. It was defined as the initial systemic or oral chemotherapy administered. This information is reported to the CCR by each treating facility where the patient was seen and is contained in unstructured free text fields. We manually reviewed treatment text fields to determine treatment type.

The treatments identified in the text fields were grouped into six clinically meaningful categories that align with NCCN treatment guidelines (3) as follows: 1) platinum doublets (any platinum chemotherapy in combination with another chemotherapy drug, excluding pemetrexed and bevacizumab); 2) pemetrexed-based combinations (pemetrexed alone or combined with a platinum agent); 3) bevacizumab-based combinations (bevacizumab alone or combined with platinum chemotherapy or another chemotherapeutic drug excluding pemetrexed; 4) pemetrexed plus bevacizumab (used together or with a platinum agent); 5) single agent (platinum or nonplatinum); 6) tyrosine kinase inhibitors (TKIs). If the treatment text fields indicated that systemic treatment was given but the drug name was missing, then treatment was categorized as systemic treatment NOS. If treatment text fields were blank or noninformative, then treatment was categorized as unknown. Treatment was categorized as "none" only when there was indication that none was given.

Outcomes

OS was the primary outcome, calculated as days from the date of diagnosis to the date of death or date of last follow-up through 2017.

Statistical Analyses

Analyses were conducted using SAS software version 9.4 (SAS Institute Inc, Cary, NC). Sociodemographic and clinical characteristics of NSCLC patients are presented by receipt of each treatment group. We used multivariable multinomial logistic regression to evaluate the association of patient characteristics and receipt of treatments. OS was estimated using the Kaplan-Meier method within treatment groups. Log-rank tests were used to assess statistically significant differences in OS between treatment groups. Multivariable Cox proportional hazards regression analysis was performed for OS by treatment groups adjusting for variables likely to be associated with the receipt of treatment and OS. Treatment was considered as a time-dependent variable and created in the regression models based on the number of days between diagnosis and initiation of treatment. Subgroup analyses by age group (younger than 70 years, 70 years and older), by squamous histology, and using different treatment reference groups were conducted. Sensitivity analyses were performed combining unknown and no treatment.

We assessed the proportional hazards assumption by plotting the log of negative log of the Kaplan-Meier estimates of the survival function vs the log of time for all predictor variables. We tested for interactions among variables of interest and assessed model goodness of fit.

Results

Of the 17 254 patients in our study, 82% had nonsquamous and 18% had squamous histology. Specific treatment information was found for 78% of the study population, and 51% of patients were known to have received first-line treatment. For patients with nonsquamous histology, the most common treatment was pemetrexed-based regimens (14.8%) followed by TKIs (11.9%) and platinum doublets (11.5%). Few patients received pemetrexed plus bevacizumab combinations (4.5%), bevacizumab-based combinations (3.6%), or single agents (1.7%). For patients with squamous histology, the most common treatment was platinum doublets (33.7%) (Table 1).

Systemic treatment choice varied by patient demographic and clinical characteristics. Patients taking pemetrexed regimens (with or without bevacizumab) or TKIs were more likely to reside in the highest SES neighborhoods and to be treated at NCI-designated cancer centers. TKI users were more likely to be female and Asian/Pacific Islander and to live in an urban area. Untreated patients were older, had more comorbidity, resided in lower SES neighborhoods, were more likely to have public insurance, and were less likely to be treated at NCI-designated cancer centers (Table 1).

Table 2 shows the results of multivariable multinomial logistic regression analysis. Patients in the lowest SES quintile had statistically significantly decreased odds of receiving platinum doublets (odds ratio [OR] = 0.79, 95% confidence interval [CI] = 0.64 to 0.97), pemetrexed-based regimens without or with bevacizumab (OR = 0.47, 95% CI = 0.38 to 0.57 without bevacizumab; OR = 0.40, 95% CI = 0.29 to 0.54 with bevacizumab), bevacizumab-based regimens (OR = 0.60, 95% CI = 0.43 to 0.85), or TKIs (OR = 0.30, 95% CI = 0.24 to 0.37) compared with those in the highest SES quintile. The odds of receiving most treatments decreased with increasing age and increasing comorbidity. Patients with Medicaid/public insurance (vs private/military) and patients treated at non-NCI-designated centers were less likely to receive most treatments.

Kaplan-Meier survival curves showed differences in survival among the treatment groups examined. TKIs conferred the longest median survival at 18.7 months followed by pemetrexed plus bevacizumab-based regimens (14.6 months), bevacizumab-based regimens (12.8 months), pemetrexed-based regimens (10.9 months), platinum doublets (8.5 months), and single agents (7.1 months). Median survival was shortest in the untreated group of patients (2.0 months) (Figure 1).

Multivariable Cox proportional hazards regression analysis for patients with nonsquamous NSCLC showed statistically significantly better OS for pemetrexed-based regimens (HR = 0.86, 95% CI = 0.80 to 0.92), bevacizumab-based regimens (HR = 0.73, 95% CI = 0.65 to 0.81), pemetrexed plus bevacizumab-based regimens (HR = 0.68, 95% CI = 0.61 to 0.76), and TKIs (HR = 0.62, 95% CI = 0.57 to 0.67) compared with platinum doublets. Single agents were associated with statistically significantly worse OS compared with platinum doublets (HR = 1.23, 95% CI = 1.06 to 1.43) (Table 3). However, single agents were associated with a better OS compared with no treatment (HR = 0.84, 95% CI = 0.73 to 0.97) (Table 4). TKIs, bevacizumab combinations, and pemetrexed plus bevacizumab combinations were associated with better OS compared with pemetrexed combinations without bevacizumab (HR = 0.72, 95% CI = 0.66 to 0.78 for TKIs; HR = 0.86, 95% CI = 0.77 to 0.96 for bevacizumab combinations; HR = 0.81, 95% CI = 0.73 to 0.89 for pemetrexed plus bevacizumab) (Table 4). Male sex, black, Hispanic, and white race/ethnicity (compared with Asian/Pacific Islander), decreasing SES quintiles, public insurance, age 65 years and older, increasing comorbidity score, treatment at non-NCI-designated cancer centers, and care not involving radiation treatment were found to be associated with a higher risk of death (Table 3).

Analysis by age group showed similar results to the model that included all ages, with the exception that in the 70 years or older age group, pemetrexed-based regimens and single agents did not have statistically significantly different OS compared with platinum doublets (Table 4). Pemetrexed-based regimens were associated with better OS compared with no treatment in this age group (HR = 0.63, 95% CI = 0.58 to 0.70). For patients with squamous histology, single agents did not have statistically significantly different OS compared to platinum doublets (HR = 1.15, 95% CI = 0.91 to 1.45).

In sensitivity analyses with the unknown treatment group combined with the no treatment group, the hazard ratio was slightly lower than the no treatment group alone (HR = 2.15, 95% CI = 2.02 to 2.28 vs HR = 2.55, 95% CI = 2.39 to 2.72 for no treatment group) (Supplementary Table A1, available online).

Discussion

Research advances in the last two decades have shed light on the biology and pathophysiology of NSCLC and resulted in the development of numerous new therapies. Accordingly, we sought to determine the utilization of systemic treatments in a real-world setting that includes patients treated across all facilities in California. We found that many patients with stage IV disease did not receive such treatment. Consistent with other studies, the most common treatment was pemetrexed-based regimens among patients with nonsquamous histology (23,42) and platinum doublets among patients with squamous histology (23). We observed a fairly low use of bevacizumab. We found differences in survival by treatment group after controlling for time to treatment and known confounders (age, comorbidity, SES, insurance type, NCI hospital status, and race/ethnicity).

Table 1. Characteristics of stage IV NSCLC patients by treatment type, 2012–2014, California*

Characteristic	Platinum doublets No. (%)	Pemetrexed based No. (%)	Bevacizumab based No. (%)	Pemetrexed + bevacizumab No. (%)	Single agents No. (%)	TKIs No. (%)	Chemo NOS No. (%)	No treatment No. (%)	Unknown No. (%)	All No. (%)
	2680 (15.5)	2114 (12.2)	530 (3.1)	635 (3.7)	324 (1.9)	1711 (9.9)	812 (4.7)	5468 (31.7)	2980 (17.3)	17 254 (100)
Sex										
Male	1563 (17.2)	1111 (12.2)	281 (3.1)	298 (3.3)	187 (2.1)	643 (7.1)	440 (4.8)	2936 (32.3)	1643 (18.1)	9102 (52.8)
Female	1117 (13.7)	1003 (12.3)	249 (3.1)	337 (4.1)	137 (1.7)	1068 (13.1)	372 (4.6)	2532 (31.1)	1337 (16.4)	8152 (47.2)
Race/ethnicity										
NH white	1765 (16.4)	1333 (12.4)	346 (3.2)	459 (4.3)	221 (2.1)	698 (6.5)	526 (4.9)	3597 (33.5)	1804 (16.8)	10 749 (62.3)
NH black	246 (17.1)	198 (13.8)	48 (3.3)	24 (1.7)	26 (1.8)	63 (4.4)	65 (4.5)	476 (33.2)	290 (20.2)	1436 (8.3)
Hispanic	318 (14.4)	255 (11.5)	57 (2.6)	63 (2.8)	42 (1.9)	213 (9.6)	115 (5.2)	708 (32.0)	444 (20.1)	2215 (12.8)
API	329 (12.2)	303 (11.2)	76 (2.8)	84 (3.1)	31 (1.2)	724 (26.8)	103 (3.8)	650 (24.0)	404 (14.9)	2704 (15.7)
Unknown	22 (14.7)	25 (16.7)	3 (2.0)	5 (3.3)	4 (2.7)	13 (8.7)	3 (2.0)	37 (24.7)	38 (25.3)	150 (0.9)
SES (quintiles)										
1 (low)	425 (14.7)	259 (9.0)	75 (2.6)	77 (2.7)	58 (2.0)	159 (5.5)	154 (5.3)	1084 (37.5)	597 (20.7)	2888 (16.7)
2	592 (16.8)	373 (10.6)	102 (2.9)	102 (2.9)	56 (1.6)	287 (8.1)	158 (4.5)	1200 (34.0)	660 (8.7)	3530 (20.5)
3	636 (17.2)	453 (12.2)	116 (3.1)	121 (3.3)	58 (1.6)	340 (9.2)	185 (5.0)	1198 (32.3)	596 (16.1)	3703 (21.5)
4	558 (14.8)	515 (13.7)	128 (3.4)	144 (3.8)	94 (2.5)	412 (10.9)	182 (4.8)	1129 (29.9)	609 (16.2)	3771 (21.9)
5 (high)	469 (14.0)	514 (15.3)	109 (3.2)	191 (5.7)	58 (1.7)	513 (15.3)	133 (3.9)	857 (25.5)	518 (15.4)	3362 (19.5)
Insurance type										
Private/military	1579 (16.6)	1313 (13.8)	349 (3.7)	390 (4.1)	174 (1.8)	1061 (11.1)	405 (4.3)	2737 (28.7)	1525 (16.0)	9533 (55.3)
Medicare	213 (13.9)	174 (11.3)	31 (2.0)	60 (3.9)	30 (1.9)	132 (8.6)	67 (4.4)	567 (36.9)	264 (17.2)	1538 (8.9)
Medicaid/public	839 (14.3)	595 (10.2)	141 (2.4)	179 (3.1)	116 (1.9)	496 (8.5)	319 (5.5)	2050 (35.0)	1115 (19.1)	5850 (33.9)
Unknown	49 (14.7)	32 (9.6)	9 (2.7)	6 (1.8)	4 (1.2)	22 (6.6)	21 (6.3)	114 (34.2)	76 (22.8)	333 (1.9)
Rural/urban										
Rural	435 (17.5)	274 (11.0)	80 (3.2)	100 (4.0)	58 (2.3)	160 (6.4)	144 (5.8)	834 (33.5)	407 (16.3)	2492 (14.4)
Urban	2245 (15.2)	1840 (12.5)	450 (3.1)	535 (3.6)	266 (1.8)	1551 (10.5)	668 (4.5)	4634 (31.4)	2573 (17.4)	14 762 (85.6)
Age group, y										
20–49	131 (18.1)	120 (16.6)	32 (4.4)	45 (6.2)	9 (1.2)	161 (22.3)	43 (5.9)	101 (14.0)	81 (11.2)	723 (4.2)
50–64	949 (19.8)	718 (14.9)	228 (4.8)	239 (4.9)	72 (1.5)	556 (11.6)	229 (4.8)	1094 (22.8)	714 (14.9)	4799 (27.8)
65 plus	1600 (13.6)	1276 (10.9)	270 (2.3)	351 (2.9)	243 (2.1)	994 (8.5)	540 (4.6)	4273 (36.4)	2185 (18.6)	11 732 (68.0)
Charlson Score										
0	793 (15.2)	762 (14.6)	217 (4.2)	301 (5.8)	92 (1.8)	788 (15.1)	246 (4.7)	1263 (24.2)	752 (14.4)	5214 (30.2)
1	782 (17.3)	588 (13.0)	149 (3.3)	168 (3.7)	86 (1.9)	329 (7.3)	226 (5.0)	1414 (31.3)	779 (17.2)	4521 (26.2)
>1	713 (14.2)	416 (8.3)	101 (2.0)	95 (1.9)	106 (2.1)	287 (5.7)	234 (4.7)	2069 (41.3)	988 (19.7)	5009 (29.0)
Unknown	392 (15.6)	348 (13.9)	63 (2.5)	71 (2.8)	40 (1.6)	307 (12.2)	106 (4.2)	722 (28.8)	461 (18.4)	2510 (14.6)
NCI designation										
Yes	370 (17.2)	466 (21.7)	66 (3.1)	116 (5.4)	33 (1.5)	368 (17.1)	52 (2.4)	436 (20.3)	244 (11.3)	2151 (12.5)
No	2310 (15.3)	1648 (10.9)	464 (3.1)	519 (3.4)	291 (1.9)	1343 (8.9)	760 (5.0)	5032 (33.3)	2736 (18.1)	15 103 (87.5)
Histology										
Squamous	1062 (33.7)	14 (0.4)	26 (0.8)	2 (0.1)	92 (2.9)	33 (1.1)	178 (5.6)	1193 (37.8)	555 (17.6)	3155 (18.3)
Nonsquamous	1618 (11.5)	2100 (14.8)	504 (3.6)	633 (4.5)	232 (1.7)	1678 (11.9)	634 (4.5)	4275 (30.3)	2425 (17.2)	14 099 (81.7)
Radiation										
Yes	1330 (21.6)	917 (14.9)	226 (3.7)	263 (4.3)	153 (2.5)	695 (11.3)	355 (5.8)	1392 (22.6)	822 (13.4)	6153 (35.7)
No	1350 (12.2)	1195 (10.8)	304 (2.7)	372 (3.4)	171 (1.5)	1016 (9.2)	455 (4.1)	4067 (36.7)	2149 (19.4)	11 079 (64.2)
Unknown	0 (0)	2 (9.1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (9.1)	9 (40.9)	9 (40.9)	22 (0.1)

*API = Asian Pacific Islander; NCI = National Cancer Institute; NH = non-Hispanic; NOS = not otherwise specified; NSCLC = non-small cell lung cancer; SD = standard deviation; SES = socioeconomic status; TKI = tyrosine kinase inhibitor.

Table 2. Multivariable-adjusted* OR and 95% CI estimates for characteristics associated with systemic treatment type among stage IV nonsquamous NSCLC patients, 2012–2014, California*

Characteristics	Treatment type (vs no systemic treatment)					
	Platinum doublets OR (95% CI)	Pemetrexed based OR (95% CI)	Bevacizumab based OR (95% CI)	Pemetrexed + bevacizumab OR (95% CI)	Single agents OR (95% CI)	TKIs OR (95% CI)
Sex: female (reference)						
Male	1.10 (0.98 to 1.24)	1.07 (0.96 to 1.19)	1.12 (0.93 to 1.35)	0.92 (0.77 to 1.09)	1.16 (0.89 to 1.52)	0.55 (0.48 to 0.62)
Race/ethnicity: API (reference)						
Black	0.93 (0.72 to 1.21)	1.17 (0.92 to 1.48)	1.01 (0.68 to 1.51)	0.51 (0.32 to 0.83)	1.70 (0.89 to 3.22)	0.17 (0.12 to 0.23)
Hispanic	1.05 (0.83 to 1.32)	1.08 (0.87 to 1.34)	0.86 (0.59 to 1.26)	0.93 (0.65 to 1.33)	1.90 (1.07 to 3.38)	0.39 (0.32 to 0.48)
Non-Hispanic white	0.92 (0.77 to 1.11)	0.91 (0.77 to 1.07)	0.90 (0.68 to 1.19)	1.11 (0.85 to 1.44)	1.45 (0.89 to 2.36)	0.19 (0.16 to 0.22)
Other-unknown	1.04 (0.48 to 2.26)	2.05 (1.12 to 3.76)	0.95 (0.28 to 3.29)	1.38 (0.50 to 3.80)	3.46 (0.95 to 12.59)	0.44 (0.22 to 0.90)
Neighborhood SES: 5 (highest SES) (reference)						
4	0.91 (0.75 to 1.10)	0.83 (0.70 to 0.97)	0.93 (0.70 to 1.23)	0.62 (0.48 to 0.79)	1.16 (0.78 to 1.73)	0.66 (0.55 to 0.79)
3	0.95 (0.78 to 1.14)	0.70 (0.59 to 0.83)	0.82 (0.61 to 1.09)	0.50 (0.39 to 0.65)	0.71 (0.46 to 1.09)	0.53 (0.44 to 0.63)
2	1.01 (0.83 to 1.23)	0.64 (0.53 to 0.76)	0.71 (0.52 to 0.97)	0.47 (0.36 to 0.62)	0.73 (0.47 to 1.14)	0.51 (0.42 to 0.62)
1 (lowest SES)	0.79 (0.64 to 0.97)	0.47 (0.38 to 0.57)	0.60 (0.43 to 0.85)	0.40 (0.29 to 0.54)	0.66 (0.40 to 1.07)	0.30 (0.24 to 0.37)
Insurance type: private/military (reference)						
Medicare	0.86 (0.69 to 1.08)	0.91 (0.75 to 1.11)	0.68 (0.46 to 1.01)	1.17 (0.87 to 1.59)	0.96 (0.60 to 1.53)	0.95 (0.75 to 1.19)
Medicaid/public	0.71 (0.62 to 0.81)	0.64 (0.57 to 0.73)	0.58 (0.47 to 0.72)	0.70 (0.58 to 0.86)	0.91 (0.68 to 1.23)	0.60 (0.52 to 0.69)
Unknown	0.62 (0.40 to 0.94)	0.48 (0.32 to 0.74)	0.52 (0.26 to 1.05)	0.31 (0.13 to 0.72)	0.31 (0.08 to 1.27)	0.44 (0.26 to 0.72)
Rural/urban residence: urban (reference)						
Rural	0.95 (0.80 to 1.14)	0.97 (0.83 to 1.15)	1.04 (0.79 to 1.37)	1.20 (0.94 to 1.53)	1.41 (0.99 to 2.01)	0.93 (0.76 to 1.15)
Age group, 20–49 (reference), y						
50–64	0.67 (0.49 to 0.91)	0.68 (0.50 to 0.92)	0.73 (0.47 to 1.12)	0.59 (0.39 to 0.87)	0.95 (0.39 to 2.27)	0.51 (0.38 to 0.69)
65 plus	0.30 (0.22 to 0.40)	0.39 (0.29 to 0.52)	0.28 (0.18 to 0.43)	0.25 (0.17 to 0.37)	0.88 (0.38 to 2.07)	0.29 (0.22 to 0.40)
Charlson Comorbidity Score: 0 (reference)						
1	0.93 (0.79 to 1.09)	0.87 (0.76 to 1.01)	0.75 (0.59 to 0.94)	0.63 (0.51 to 0.78)	0.78 (0.55 to 1.12)	0.55 (0.47 to 0.65)
>1	0.76 (0.65 to 0.89)	0.49 (0.42 to 0.57)	0.42 (0.32 to 0.55)	0.30 (0.24 to 0.39)	0.73 (0.51 to 1.03)	0.40 (0.33 to 0.47)
Unknown	1.00 (0.83 to 1.22)	0.99 (0.84 to 1.18)	0.61 (0.45 to 0.83)	0.53 (0.40 to 0.70)	0.91 (0.59 to 1.41)	0.83 (0.69 to 1.00)
NCI-designated center: yes (reference)						
No	0.63 (0.52 to 0.76)	0.36 (0.30 to 0.42)	0.73 (0.55 to 0.98)	0.49 (0.39 to 0.63)	1.10 (0.68 to 1.79)	0.43 (0.36 to 0.51)
Radiation: yes (reference)						
No	0.36 (0.32 to 0.40)	0.52 (0.46 to 0.58)	0.54 (0.45 to 0.66)	0.61 (0.51 to 0.73)	0.40 (0.30 to 0.52)	0.57 (0.50 to 0.65)

*Adjusted for all variables in the table. API = Asian Pacific Islander; CI = confidence interval; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; OR = odds ratio; SES = socioeconomic status; TKI = tyrosine kinase inhibitor.

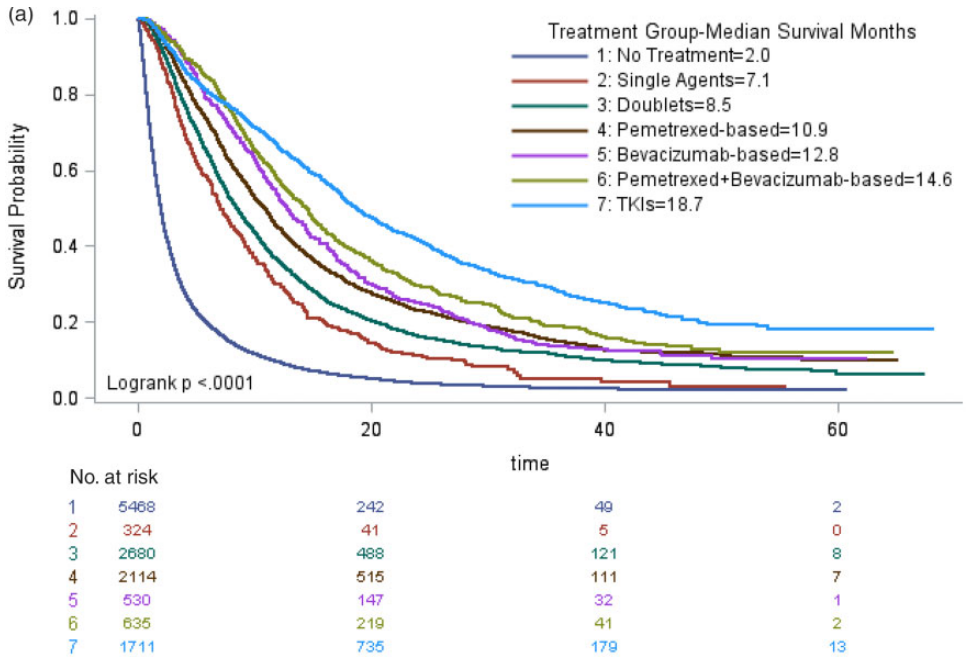

Figure 1. Survival curves of systemic treatment groups.

All treatment groups except single agents had better OS compared with platinum doublets. Consistent with clinical trial findings and other studies (16,20,22), TKIs and bevacizumab combinations had better OS compared with other treatments. We found that patients of all ages benefited from all treatments. Finally, we found disparities in treatment use by SES, insurance type, age, and NCI status of treating institution.

From this retrospective observational study, it is difficult to thoroughly evaluate the indications and rationales of specific treatments without knowing more about patient characteristics such as performance status, contraindications to certain treatments, and biomarker test results. However, the utilization of some of the treatments appears to be low. It is estimated that approximately 24% of nonsquamous tumors have TKI actionable mutations (15% EGFR, 7% ALK, and 2% ROS1) (6,43). We observed that TKIs were used by only 11.9% of patients with nonsquamous histology. Consistent with other studies, patients taking TKIs were more likely to be female or Asian/Pacific Islander, groups found to have a higher prevalence of EGFR mutations (22,44,45). Low use could represent delays in incorporating recommended guidelines into clinical practice. Likewise, bevacizumab use (8.1%) also appears low. Patient factors that we were unable to evaluate (performance status, anticoagulation therapy, and brain metastases) likely influenced its use. Recent studies on bevacizumab indicate that the only absolute contraindications to its use are squamous histology and a history of clinically significant hemoptysis, but there are no biomarkers that can predict a favorable response to treatment (46,47). Other barriers to use that have been cited include lack of reimbursement and high out-of-pocket costs (48), reasons that could help explain the statistically significantly decreased odds (roughly one-half) of receiving bevacizumab and other treatments for low neighborhood SES patients (vs high neighborhood SES) in our study.

The high percentage of patients receiving no systemic treatment in our study is consistent with other studies that have found proportions of untreated patients with advanced stage disease ranging from 25% to 46% (49–51). Similar to findings from other studies, a higher proportion of untreated patients resided in low SES neighborhoods, had comorbidities, were older, had non-private insurance, and were seen at non-NCI-designated facilities compared with treated patients (27,51–62). Of note, patients with Medicaid/public insurance (vs private/military insurance) were 30–40% less likely to receive most treatments and patients treated at non-NCI-designated centers were 30–60% less likely to receive most treatments.

Our observation that very few patients with squamous histology were taking pemetrexed, bevacizumab, or TKIs is consistent with NCCN guidelines that patients with squamous histology usually do not benefit from these drugs (3).

Our study showed that patients aged 70 years and older did benefit from all treatments, but treatment use declined with increasing age. Because elderly patients are underrepresented in clinical trials, there is uncertainty regarding drug efficacy and toxicity in this population and undertreatment has been noted (51,63,64). Given that forgoing treatment is associated with a very poor outcome and newer treatments can be easier to tolerate, all patients should be counseled about their treatment options.

There are several limitations to our study. First, there is a high percentage of patients with unknown treatment. However, sensitivity analysis results suggest that the unknown group may be largely composed of untreated patients. Second, we were unable to assess the use of immune checkpoint inhibitors (eg, pembrolizumab) that target PD-L1 because approval of this class of drug occurred after the study years examined in this analysis (12,13). Third, we lack information that is important in treatment selection such as performance status, biomarker testing results, and patient characteristics that may contraindicate treatments. Fourth, we were unable to assess length of treatment or subsequent treatments.

Table 3. Multivariable-adjusted* HR and 95% CI estimates for OS for treatment groups, stage IV nonsquamous NSCLC, 2012–2014, California

Characteristic	HR (95% CI)	P
Treatment group: platinum doublets (reference)		
Pemetrexed-based	0.86 (0.80 to 0.92)	<.001
Bevacizumab-based	0.73 (0.65 to 0.81)	<.001
Pemetrexed + bevacizumab-based	0.68 (0.61 to 0.76)	<.001
Single agents	1.23 (1.06 to 1.43)	.007
TKIs	0.62 (0.57 to 0.67)	<.001
Sex: female (reference)		
Male	1.24 (1.19 to 1.30)	<.001
Race/ethnicity: API (reference)		
Black	1.25 (1.14 to 1.37)	<.001
Hispanic	1.20 (1.11 to 1.30)	<.001
Non-Hispanic white	1.33 (1.25 to 1.42)	<.001
Other-unknown	0.93 (0.72 to 1.20)	.56
Neighborhood SES: 5 (highest SES) (reference)		
4	1.07 (1.00 to 1.14)	.05
3	1.13 (1.06 to 1.21)	<.001
2	1.09 (1.02 to 1.16)	.02
1 (Lowest SES)	1.21 (1.12 to 1.30)	<.001
Insurance type: private/military (reference)		
Medicare	1.09 (1.01 to 1.07)	.02
Medicaid	1.12 (1.06 to 1.16)	<.001
Unknown	1.11 (0.96 to 1.30)	.17
Rural/urban residence: urban (reference)		
Rural	1.01 (0.95 to 1.07)	.86
Age: 20–49 y (reference)		
50–64	1.03 (0.93 to 1.15)	.56
65 and over	1.18 (1.06 to 1.30)	.003
Charlson Comorbidity Score: 0 (reference)		
1	1.28 (1.21 to 1.35)	<.001
>1	1.43 (1.36 to 1.52)	<.001
Unknown	0.85 (0.79 to 0.90)	<.001
NCI designated center: yes (reference)		
No	1.42 (1.33 to 1.51)	<.001
Radiation: yes (reference)		
No	1.15 (1.10 to 1.20)	<.001
Unknown	3.45 (1.85 to 6.43)	<.001

*Adjusted for all variables in the table. API = Asian Pacific Islander; CI = confidence interval; HR = hazard ratio; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; OS = overall survival; SES = socioeconomic status; TKI = tyrosine kinase inhibitor.

Table 4. Multivariable-adjusted* HR and 95% CI estimates for OS for treatment groups by subgroups, stage IV NSCLC, 2012–2014, California

Group	HR (95% CI)	P
Nonsquamous		
Age under 70 y: platinum doublets (reference)		
Pemetrexed-based	0.83 (0.75 to 0.91)	<.001
Bevacizumab-based	0.71 (0.62 to 0.82)	<.001
Pemetrexed + bevacizumab-based	0.66 (0.58 to 0.76)	<.001
Single agents	1.58 (1.24 to 2.00)	<.001
TKIs	0.51 (0.46 to 0.57)	<.001
Age 70 y and over: platinum doublets (reference)		
Pemetrexed-based	0.90 (0.80 to 1.01)	.08
Bevacizumab-based	0.76 (0.63 to 0.93)	.007
Pemetrexed + bevacizumab-based	0.74 (0.62 to 0.88)	<.001
Single agents	1.08 (0.89 to 1.32)	.44
TKIs	0.75 (0.66 to 0.85)	<.001
Age 70 y and over: no treatment (reference)		
Platinum doublets	0.70 (0.63 to 0.78)	<.001
Pemetrexed-based	0.63 (0.58 to 0.70)	<.001
Bevacizumab-based	0.54 (0.45 to 0.65)	<.001
Pemetrexed + bevacizumab-based	0.52 (0.44 to 0.61)	<.001
Single agents	0.76 (0.63 to 0.91)	.003
TKIs	0.53 (0.48 to 0.58)	<.001
All ages: no treatment (reference)		
Platinum doublets	0.71 (0.67 to 0.76)	<.001
Pemetrexed-based	0.61 (0.57 to 0.65)	<.001
Bevacizumab-based	0.52 (0.47 to 0.58)	<.001
Pemetrexed + bevacizumab-based	0.49 (0.44 to 0.54)	<.001
Single agents	0.84 (0.73 to 0.97)	.02
TKIs	0.44 (0.40 to 0.47)	<.001
All ages: pemetrexed-based (reference)		
Platinum doublets	1.17 (1.09 to 1.26)	<.001
Bevacizumab-based	0.86 (0.77 to 0.96)	.006
Pemetrexed + bevacizumab-based	0.81 (0.73 to 0.89)	<.001
Single agents	1.38 (1.19 to 1.61)	<.001
TKIs	0.72 (0.66 to 0.78)	<.001
Squamous		
All ages: platinum doublets (reference)		
Single agents	1.15 (0.91 to 1.45)	.24

*Adjusted for sex, race/ethnicity, insurance type, rural/urban residence, age at diagnosis, neighborhood SES, comorbidity score, NCI facility, and radiation treatment. CI = confidence interval; HR = hazard ratio; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; OS = overall survival; SES = socioeconomic status; TKI = tyrosine kinase inhibitor.

Finally, because there is the potential for biased results due to differences in patient characteristics between treatment groups, we did subanalyses using propensity score methodology (described in the Supplementary Appendix, available online) to balance the baseline covariates between patients receiving any treatment vs no treatment and patients receiving bevacizumab or TKIs vs other chemotherapy. Results are displayed as Kaplan-Meier survival curves and hazard ratios and their associated 95% confidence intervals (Supplementary Figures A2 and A3; Supplementary Tables A2 and A3, available online). The propensity score matching confirmed our finding that patients receiving bevacizumab or TKIs had a survival advantage over patients receiving other systemic treatments that cannot be attributed to differences in comorbidity, age, sex, race/ethnicity, treating facility (NCI designation), and neighborhood SES. It also revealed that many untreated patients were statistically similar to treated patients and might have benefited from treatment.

Despite these limitations, our study was able to harness little used data from text fields to get population-wide information on treatment use and outcomes. Our study included adults of all ages, patients at all hospital types, and all classes of treatments recommended during the study years, making this a comprehensive assessment of stage IV NSCLC treatment utilization in a US population. The inclusion of all hospital types is a

major strength of this study. Spence et al. described treatment patterns and survival but only in Kaiser patients, approximately 20% of our study population. Treatment use and outcomes among all patients can extend clinical trial findings and inform researchers and clinicians about effectiveness in all patient types.

Treatment for NSCLC is rapidly evolving, and guidelines are changing quickly as more treatments are introduced. This study showed that there has been modest use of treatments, especially among persons with low SES, indicating possible financial and educational barriers to receiving treatment. This is consistent with several other recent reports showing worse outcomes and lower quality of cancer care for uninsured and publicly insured patients (65–68). Further research is warranted to better understand patient and provider barriers to the use of effective treatments among NSCLC patients and the role of health insurance in determining which treatment is received.

Funding

This work was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the NCI's Surveillance, Epidemiology, and End Results Program under contracts awarded to the Cancer Prevention Institute of California, the University of Southern California, and the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement awarded to the California Department of Public Health. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California, Department of Public Health, the NCI, the Centers for Disease Control and Prevention, or their Contractors and Subcontractors is not intended nor should be inferred.

Notes

Affiliations of authors: California Cancer Reporting and Epidemiologic Surveillance Program, Institute for Population Health Improvement, University of California Davis, Davis, CA (FBM, CRM, APP, KWK); Graduate Group in Epidemiology, University of California Davis, Davis, CA (FBM); Department of Public Health Sciences, University of California Davis, Davis, CA (RDC); Center for Oncology Hematology Outcomes Research and Training (COHORT), and Division of Hematology and Oncology, University of California Davis School of Medicine (THMK, PSL); School of Nursing, State University of New York, University of Buffalo, Buffalo, NY (CSL); Department of Emergency Medicine, University of California Davis School of Medicine, Davis, CA (KWK); Betty Irene Moore School of Nursing, University of California Davis, Davis, CA (KWK).

References

1. National Cancer Institute. SEER Cancer Statistics Fact Sheets: Lung and Bronchus Cancer Bethesda, Maryland 2016. https://seer.cancer.gov/statfacts/html/lungb.html. Accessed December 12, 2017.
2. Howlander NN, Krapcho M, Miller D, et al. SEER Cancer Statistics Review, 1975-2014. October 4, 2017. https://seer.cancer.gov/csr/1975_2014/ based on November 2016 SEER data submission. Accessed December 12, 2017.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 9.2017. 2017. Accessed January 24, 2018. Published by Harborside Press, LLC in Cold Spring Harbor, New York.
4. D'Addario G, Pintilie M, Leighl NB, et al. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. *J Clin Oncol*. 2005;23(13):2926–2936.
5. Rossi A, Di Maio M. Platinum-based chemotherapy in advanced non-small-cell lung cancer: optimal number of treatment cycles. *Expert Rev Anticancer Therapy*. 2016;16(6):653–660.
6. Hirsch FR, Suda K, Wiens J, et al. New and emerging targeted treatments in advanced non-small-cell lung cancer. *Lancet*. 2016;388(10048):1012–1024.
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 3.2012. 2012. Accessed January 24, 2018. Harborside Press, LLC in Cold Spring Harbor, New York.
8. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 2.2013. 2013. Accessed January 24, 2018. Published by Harborside Press, LLC in Cold Spring Harbor, New York.
9. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 3.2014. 2014. Accessed January 24, 2018. Published by Harborside Press, LLC in Cold Spring Harbor, New York.
10. Keedy VL, Temin S, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: epidermal growth factor receptor (EGFR) mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. *J Clin Oncol*. 2011;29(15):2121–2127.
11. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Mol Diagn*. 2013;15(4):415–453.
12. Reck M. Pembrolizumab as first-line therapy for metastatic non-small-cell lung cancer. *Immunotherapy*. 2018;10(2):93–105.
13. U.S. Food and Drug Administration. Pembrolizumab (Keytruda) 5-10-2017: U.S. Department of Health and Human Services; 2017. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm558048.htm. Accessed February 8, 2018.
14. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371(21):1963–1971.
15. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371(23):2167–2177.
16. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355(24):2542–2550.
17. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010;362(25):2380–2388.
18. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368(25):2385–2394.
19. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008;26(21):3543–3551.
20. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12(8):735–742.
21. Enewold L, Thomas A. Real-world patterns of EGFR testing and treatment with erlotinib for non-small cell lung cancer in the United States. *PLoS One*. 2016;11(6):e0156728.
22. Spence MM, Hui RL, Chang JT, et al. Treatment patterns and overall survival associated with first-line systemic therapy for patients with advanced non-small cell lung cancer. *JMCP*. 2017;23(2):195–205.
23. Abernethy AP, Arunachalam A, Burke T, et al. Real-world first-line treatment and overall survival in non-small cell lung cancer without known EGFR mutations or ALK rearrangements in US community oncology setting. *PLoS One*. 2017;12(6):e0178420.
24. Sacher AG, Le LW, Lau A, et al. Real-world chemotherapy treatment patterns in metastatic non-small cell lung cancer: are patients undertreated? *Cancer*. 2015;121(15):2562–2569.
25. Isobe H, Mori K, Minato K, et al. Real-world practice patterns for patients with advanced non-small cell lung cancer: multicenter retrospective cohort study in Japan. *LCTT*. 2017;8:191–206.
26. Verleye L, De Gendt C, Vrijens F, et al. Patterns of care for non-small cell lung cancer patients in Belgium: a population-based study. *Eur J Cancer Care*. 2017.
27. Younis T, Al-Fayea T, Virik K, et al. Adjuvant chemotherapy uptake in non-small cell lung cancer. *J Thorac Oncol*. 2008;3(11):1272–1278.
28. Cancer Reporting in California: California Reporting System Standards, *Volume I: Abstracting and Coding Procedures*. In: *California Department of Public Health*, 17th ed. Sacramento, CA: Chronic Disease Surveillance and Research Branch; April 2017. Accessed December 16, 2017.
29. Cancer Reporting in California: Standards for Automated Reporting. *California Cancer Reporting System Standards, Volume II*. In: California Department of Public Health. Sacramento, CA: Chronic Disease Surveillance and Research Branch; April 2016. Accessed December 16, 2017.

30. Cancer Reporting in California: Data Standards for Regional Registries and California Cancer Registry. *California Cancer Reporting System Standards, Volume III*. In: California Department of Public Health. Sacramento, CA: Chronic Disease Surveillance and Research Branch; April 2017. Accessed December 16, 2017.
31. *Physician Requirements for Cancer Reporting in California: Volume IV*. In: California Department of Public Health. Sacramento, CA: Chronic Disease Surveillance and Research Branch; November 2016. Accessed December 16, 2017.
32. NCI Surveillance Epidemiology and End Results Program. Site Recode ICD-O-3/WHO 2008 Definition 2017. https://seer.cancer.gov/siterecode/icdo3_dwhoheme/. Accessed December 15, 2017.
33. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol*. 2015;10(9):1243–1260.
34. North American Association of Central Cancer Registries. NAACCR Hispanic and Asian/Pacific Islander Identification Algorithm (NHAPIIA); 2017. https://www.naaccr.org/analysis-and-data-improvement-tools/#NHAPIIA. Accessed December 15, 2017.
35. Yang JS, Harrati A, Clarke C, Keegan THM, Gomez SL. *Developing an Area-Based Socioeconomic Measure from American Community Survey Data*. Fremont, CA: Cancer Prevention Institute of California; 2014.
36. Bradley CJ, Gardiner J, Given CW, et al. Cancer, medicaid enrollment, and survival disparities. *Cancer*. 2005;103(8):1712–1718.
37. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613–619.
38. Lichtensztajn DY, Giddings BM, Morris CR, et al. Comorbidity index in central cancer registries: the value of hospital discharge data. *CLEP*. 2017;9:601–609.
39. Sharabi AB, Nirschl CJ, Kochel CM, et al. Stereotactic radiation therapy augments antigen-specific PD-1-mediated antitumor immune responses via cross-presentation of tumor antigen. *Cancer Immunol Res*. 2015;3(4):345–355.
40. Voong KR, Naidoo J, Ettinger DS. The next frontier in non-small cell lung cancer: synergizing radiation therapy and immune checkpoint blockade. *Clin Adv Hematol Oncol: H&O*. 2017;15(8):615–625.
41. Pastina P, Nardone V, Botta C, et al. Radiotherapy prolongs the survival of advanced non-small-cell lung cancer patients undergone to an immune-modulating treatment with dose-fractioned cisplatin and metronomic etoposide and bevacizumab (mPEBev). *Oncotarget*. 2017;8(44):75904–75913.
42. Zhou Q, Song Y, Zhang X, et al. A multicenter survey of first-line treatment patterns and gene aberration test status of patients with unresectable Stage IIIB/IV nonsquamous non-small cell lung cancer in China (CTONG 1506). *BMC Cancer*. 2017;17(1):462.
43. Greenhalgh J, Dwan K, Boland A, et al. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. *Cochrane Database Syst Rev*. 2016;(5):Cd010383.
44. Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII.). *Am J Canc Res*. 2015;5(9):2892–2911.
45. Shi Y, Au JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol*. 2014;9(2):154–162.
46. Russo AE, Priolo D, Antonelli G, et al. Bevacizumab in the treatment of NSCLC: patient selection and perspectives. *Lung Cancer (Auckl)*. 2017;8:259–269.
47. Besse B, Le Moulec S, Mazieres J, et al. Bevacizumab in patients with nonsquamous non-small cell lung cancer and asymptomatic, untreated brain metastases (BRAIN): a nonrandomized, phase II study. *Clin Cancer Res*. 2015;21(8):1896–1903.
48. Monk BJ, Lammers PE, Cartwright T, et al. Barriers to the access of bevacizumab in patients with solid tumors and the potential impact of biosimilars: a physician survey. *Pharmaceuticals (Basel, Switzerland)*. 2017;10(1):19.
49. David EA, Daly ME, Li CS, et al. Increasing rates of no treatment in advanced-stage non-small cell lung cancer patients: a propensity-matched analysis. *J Thorac Oncol*. 2017;12(3):437–445.
50. Brule SY, Al-Baimani K, Jonker H, et al. Palliative systemic therapy for advanced non-small cell lung cancer: investigating disparities between patients who are treated versus those who are not. *Lung Cancer*. 2016;97:15–21.
51. Small AC, Tsao CK, Moshier EL, et al. Prevalence and characteristics of patients with metastatic cancer who receive no anticancer therapy. *Cancer*. 2012;118(23):5947–5954.
52. Berglund A, Lambe M, Luchtenborg M, et al. Social differences in lung cancer management and survival in South East England: a cohort study. *BMJ Open*. 2012;2(3).
53. Rhoads KF, Ngo JV, Ma Y, et al. Do hospitals that serve a high percentage of Medicaid patients perform well on evidence-based guidelines for colon cancer care? *J Health Care Poor Underserved*. 2013;24(3):1180–1193.
54. Aizer AA, Falit B, Mendu ML, et al. Cancer-specific outcomes among young adults without health insurance. *J Clin Oncol*. 2014;32(19):2025–2030.
55. Coburn N, Fulton J, Pearlman DN, et al. Treatment variation by insurance status for breast cancer patients. *Breast J*. 2008;14(2):128–134.
56. Pezzi TA, Schwartz DL, Mohamed ASR, et al. Barriers to combined-modality therapy for limited-stage small-cell lung cancer. *JAMA Oncol*. 2018;4(8):e174504.
57. Tabchi S, Kassouf E, Florescu M, et al. Factors influencing treatment selection and survival in advanced lung cancer. *Curr Oncol*. 2017;24(2):e115–e122.
58. Stavrou EP, Lu CY, Buckley N, et al. The role of comorbidities on the uptake of systemic treatment and 3-year survival in older cancer patients. *Ann Oncol*. 2012;23(9):2422–2428.
59. Bakirhan K, Sharma J, Perez-Soler R, et al. Medical treatment in elderly patients with non-small cell lung cancer. *Curr Treatment Options Oncol*. 2016;17(3):13.
60. Cuffe S, Booth CM, Peng Y, et al. Adjuvant chemotherapy for non-small-cell lung cancer in the elderly: a population-based study in Ontario, Canada. *J Clin Oncol*. 2012;30(15):1813–1821.
61. Ho G, Wun T, Muffly L, et al. Decreased early mortality associated with the treatment of acute myeloid leukemia at National Cancer Institute-designated cancer centers in California. *Cancer*. 2018;124(9):1938–1945.
62. Bristow RE, Chang J, Ziogas A, et al. Impact of National Cancer Institute Comprehensive Cancer Centers on ovarian cancer treatment and survival. *J Am Coll Surgeons*. 2015;220(5):940–950.
63. Denson AC, Mahipal A. Participation of the elderly population in clinical trials: barriers and solutions. *Cancer Control* 2014;21(3):209–214.
64. Shenoy P, Harugeri A. Elderly patients' participation in clinical trials. *Perspect Clin Res*. 2015;6(4):184–189.
65. Cress RD, Chen YS, Morris CR, et al. Underutilization of gene expression profiling for early-stage breast cancer in California. *Cancer Causes Control*. 2016;27(6):721–727.
66. Ellis L, Canchola AJ, Spiegel D, et al. Trends in cancer survival by health insurance status in California from 1997 to 2014. *JAMA Oncol*. 2018;4(3):317–323.
67. Parikh-Patel AM, Martinsen R, Kizer KW, *Disparities in Stage at Diagnosis, Survival, and Quality of Cancer Care in California by Source of Health Insurance*. Sacramento, CA: California Cancer Reporting and Epidemiologic Surveillance Program, Institute for Population Health Improvement, University of California Davis; 2015.
68. Parikh-Patel A, Morris CR, Kizer KW. Disparities in quality of cancer care: the role of health insurance and population demographics. *Medicine (Baltimore)*. 2017;96(50):e9125.