Evaluating the real-world use, effectiveness, and cost of cancer therapies in older adults using routinely collected data

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INTRODUCTION

The treatment approach for advanced cancer has been evolving rapidly with the introduction of novel targeted therapies and immunotherapies.[1] Despite the rapid expansion of therapeutic options, however, little is known about the real-world impact of these novel cancer treatments, particularly among elderly individuals.

First, the applicability of clinical trial findings to older adults in routine practice is often limited. Older age is associated with increased comorbidities, lower functional status, and increased toxicity of cancer treatment.[2] Nevertheless, elderly patients, who constitute the majority of patients with advanced cancer, are underrepresented in clinical trials.[2-6] Little evidence is available about the effectiveness of novel cancer treatments in this age group.

Second, the high prices of new cancer treatments are imposing a significant financial burden on the health care system. The average drug costs of novel immunotherapy, nivolumab, were estimated to be $72,589 and $77,774 for patients with non-squamous and squamous non-small cell lung cancer (NSCLC), respectively.[7] Nevertheless, little is known about how these expensive medications affect the total cost of cancer care.

Finally, understanding the effectiveness of novel cancer therapies requires creative use of routinely collected observational data gathered in real-world settings. However, despite the potential of observational studies to complement the findings of randomized trials and improve evidence-based oncology practice, their role in cancer care decision making has largely been limited by the concerns about the validity of study findings.[6,8] Evaluating whether well-designed observational studies can correctly infer cancer treatment effects despite the challenges of observational analyses can help to evaluate the role of observational studies in oncology practice.

The *long-term goal* of this dissertation is to better understand the impact of new cancer treatments, and to improve evidence-based cancer care. The *objective* of this dissertation is to determine the real-world use, effectiveness, and cost of cancer therapies that are commonly used for older adults receiving care in routine oncology practice. To accomplish this objective, this dissertation investigates a population-based sample of older adults with advanced cancer using the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database.

The first chapter of the dissertation examines the population-level clinical and financial impact of the introduction of immune checkpoint inhibitors among older adults diagnosed with advanced NSCLC between 2012 and 2015. The second chapter examines the characteristics and prognosis of older adults with advanced NSCLC receiving immune checkpoint inhibitors in routine practice, including those with poor performance status and autoimmune conditions who were excluded from the clinical trials.[9-11] The third chapter determines the comparative effectiveness of bevacizumab as first-line treatment for patients with advanced breast cancer. We compared the findings of our observational analyses with those of randomized trials to evaluate the role of observational studies in cancer care decision making. This dissertation will pursue the following specific aims in each chapter.

Aim 1. Examine trends in treatment use, survival, and cost for older adults with advanced non-small cell lung cancer after the introduction of immune checkpoint inhibitors

Aim 2. Examine the characteristics and prognosis of older adults with non-small cell lung cancer treated with immune checkpoint inhibitors in routine oncology practice

Aim 3. Compare the effectiveness of bevacizumab plus chemotherapy versus chemotherapy alone on overall survival among older women with advanced breast cancer

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CHAPTER 1. Trends in treatment patterns, overall survival, and spending for older adults with advanced non-small-cell lung cancer after the introduction of immune checkpoint inhibitors

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most common cause of death from cancer in the United States. The majority of patients with NSCLC are diagnosed at an advanced stage and are aged 65 years or older.[1,2] Prognosis of advanced NSCLC is poor; five-year relative survival probabilities are 34.5% and 6.1% for those with regional and metastatic disease, respectively.[1]

The treatment approach for advanced NSCLC substantially changed with the introduction of immune checkpoint inhibitors in 2015.[3] In the CheckMate-057 and 017 trials,[4,5] nivolumab improved overall survival by 2.8 and 3.2 months in advanced non-squamous and squamous NSCLC patients with progression on or after platinum-based chemotherapy, respectively. In the KEYNOTE-010 trial,[6] pembrolizumab improved overall survival by 1.9 months among those with positive programmed death-ligand 1 (PD-L1) mutation. Despite the clinical benefits, the use of immune checkpoint inhibitors is associated with substantial healthcare costs. The average drug costs of nivolumab treatment were estimated to be $72589 and $77774 for patients with non-squamous and squamous NSCLC, respectively.[7] The average drug cost of pembrolizumab treatment was $55188 for patients with positive PD-L1 mutation.[7]

Given the rapid adoption of these high cost therapies in routine oncology practice,[3] it is important to understand the population-level clinical and financial impact of the introduction of these therapies. A prior study found that patients treated with immune checkpoint inhibitors in routine practice are significantly older than those who participated in clinical trials,[3-6] further suggesting the need to study the impact of the rapid adoption of these treatments in routine care settings. In this study, we examined trends in treatment patterns, overall survival, and spending among older adults diagnosed with advanced NSCLC between 2012 and 2015 to describe the early clinical and financial impact of the introduction of immune checkpoint inhibitors. To determine whether the observed trends are attributable to the availability of new treatment options, we examined whether the survival and spending trends differed for patients who were likely or unlikely to receive systemic antineoplastic therapy.

METHODS

Study design and data sources

We identified patients 65 years or older who were diagnosed with pathologically confirmed first-primary stage IIIB-IV NSCLC between January 2012 and December 2015 using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data. The SEER data contain the demographic and clinical information of incident cancer cases in defined geographic areas that include approximately 30% of the U.S. population.[2,8] The Medicare data include Medicare enrollment status, survival status, and claims for beneficiaries with fee-for-service coverage. To identify baseline characteristics, we required continuous enrollment for Medicare Parts A and B fee-for-service in the 12 months prior to diagnosis. To ascertain oral targeted therapy use, we identified the subset of patients who were enrolled in Medicare Part D during the month of diagnosis. Data on Medicare claims for identifying treatment use and spending were available until December 31, 2016; data on survival status from the Medicare Enrollment Database were available until December 31, 2017.

Outcomes

Treatment use: We identified receipt of any antineoplastic therapy within two years of diagnosis by using Healthcare Common Procedure Coding System (HCPCS) codes, Current Procedural Terminology codes, and National Drug Codes (NDCs) from Medicare inpatient, outpatient, physician, and durable medical equipment files. Antineoplastic therapy included systemic chemotherapies, immune checkpoint inhibitors, and intravenous targeted therapy. For immune checkpoint inhibitors, we included non-specific HCPCS codes (C9399, J9999) for 2015 claims because several HCPCS codes for immune checkpoint inhibitors became available in July 2015 (C9453) and in January 2016 (J9299, J9271). We identified oral targeted therapies using NDCs and generic names from Part D drug event file. We provide the codes and definitions of study variables in Appendix Table 1.

Survival: We examined overall survival from diagnosis to death or December 31, 2017, whichever came first, and restricted mean survival at two years post-diagnosis (i.e., the mean survival time up to two years of follow-up).[9]

Spending: We calculated total Medicare spending within two years of diagnosis as the sum of Medicare Part A and B reimbursements for inpatient, outpatient, physician, hospice, home health care, and durable medical equipment. We included all Medicare spending because most spending would be attributable to cancer considering the advanced disease of the patients.[2] We did not include patient out-of-pocket payments. We classified the spending as acute inpatient, outpatient, or other. Outpatient spending consists of outpatient claims and physician claims from the National Claims History file, and includes spending for physician-administered antineoplastic therapy. We examined spending within two years of diagnosis, which includes spending for initial treatment and end-of-life care for the majority of patients with advanced NSCLC. We separately assessed oral prescription drug spending among patients enrolled in Medicare Part D. We examined gross drug cost (i.e., the price paid for the drug at the point-of-sale by the Medicare program, prescription drug plans, patients, and other parties). We assessed spending in 2016 dollars using the Inpatient Hospital Market Basket for Part A payments, the Medicare Economic index for Part B payments, and medical care Consumer Price Index for Part D payments.[10-12]

Covariates

We obtained information on patient age, sex, race, stage at diagnosis, histology, brain metastasis at diagnosis, original reason for Medicare entitlement, Medicaid dual eligibility, region, SEER registry, rural, marital status, and area-level poverty-level. We also extracted information on the comorbid conditions included in the Charlson score,[13,14] a proxy of performance status,[15,16] home health services use, skilled nursing facility admission, number of inpatient admissions, number of emergency room visits, annual wellness visit,[17] and flu vaccination during the year before diagnosis from Medicare claims. The proxy of performance status was based on claims for healthcare services commonly used by patients with poor performance status, such as home oxygen, wheelchair, and home health services.[15,16] We also

extracted information on care at National Cancer Institute-designated cancer center during the month prior to diagnosis. For patients who received immune checkpoint inhibitors, we extracted information on history of any antineoplastic therapy prior to immune checkpoint inhibitor receipt. We classified each patient's history as none, single agent-chemotherapy, platinum doublets with or without bevacizumab, and other.

Statistical Analysis

Treatment use: We estimated the number of patients receiving any antineoplastic therapy at each month by diagnosis year. Then, we obtained the cumulative proportion of treatment receipt during the two years following diagnosis. Patients were followed from diagnosis to any antineoplastic therapy receipt, death, censoring, or the end of the two-year follow-up, whichever came first. Death was considered as a terminal event.[18] Censoring event included administrative censoring on December 31, 2016 and changes in Medicare enrollment status (i.e., losing Part A/B coverage or enrollment in a Medicare Advantage plan). We accounted for censoring by using inverse probability of censoring weighting (IPCW) methods.[19] We estimated pooled logistic regression models for the discrete-time (monthly) hazard of censoring and used the fitted models to estimate the cumulative probability of not being censored for each month. We then used the inverse of these probabilities as weights in our analyses.[18-20] The details of these methods are described in Appendix Methods 1. We repeated the analyses for the use of immune checkpoint inhibitor, intravenous targeted therapy, and oral targeted therapy (among the subgroup of patients with Part D enrollment).

Survival: We used Kaplan–Meier methods to estimate survival curves stratified by year of diagnosis. We also estimated the one-year and two-year survival probabilities as well as 25%, median, and 75% survival, and restricted mean survival at two years.[19,21]

Spending: We estimated total spending at each month following diagnosis and used the monthly estimates to calculate the one-year and two-year cumulative mean spending per patient by year of

diagnosis. We included patient spending from diagnosis until the earliest of death, censoring, or the end of the two-year follow-up period. In spending analyses, we accounted for censoring by using the same IPCW methods (Appendix Methods 1). We repeated the analysis by spending category, including acute inpatient, outpatient, and Part D drug spending.

Subgroup analysis by the probability of any antineoplastic therapy: To determine whether trends in survival and spending vary by a patient's probability to receive systemic antineoplastic therapy, we built prediction models for the receipt of any antineoplastic therapy conditional on baseline covariates. We classified patients into quintiles based on their predicted cumulative probability of receiving treatment during the two year follow-up. To prevent overfitting of the predictive models, we randomly split patients into two groups and fitted pooled logistic regression models for any antineoplastic therapy receipt by using time from diagnosis, patient demographics and socioeconomic status, cancer characteristics, measures of health status and health services use, and provider characteristics at diagnosis. Then, we estimated the probability of treatment receipt for each patient on the basis of the prediction model created from the other random-split group (Appendix Methods 2).[22] We classified patients into quintiles on the basis of their predicted probability. We repeated the survival and spending analyses within these quintile groups, respectively.

Descriptive and exploratory analyses: We performed several stability analyses to assess the robustness of our findings. First, we examined the survival and spending trends in subgroup of patients with any antineoplastic therapy claim during the two years following diagnosis. Second, we used only specific HCPCS codes to select patients with immune checkpoint inhibitors and excluded non-specific HCPCS codes (i.e., C9399, J9999 in 2015 claims). As an exploratory analysis, we also examined spending among patients who actually received immune checkpoint inhibitors within two years of diagnosis.

For all analyses, we obtained 95% confidence intervals using the nonparametric bootstrap (500 samples). We performed analyses using SAS version 9.4 (SAS Institute Inc.) and R version 3.5.2 (R

Foundation for Statistical Computing). The Brown University Institutional Review Board waived the approval requirement for this study.

RESULTS

We identified 25841 patients who were diagnosed with advanced NSCLC between 2012 and 2015 and met the study eligibility criteria (Appendix Figure 1). Among them, 16446 patients were enrolled in Medicare Part D and contributed to Part D subgroup analyses.

Table 1 describes selected baseline patient characteristics by year of diagnosis (Appendix Table 2 presents additional characteristics). The distribution of baseline characteristics was stable during the study period. The majority of patients had stage IV disease and non-squamous histology. Approximately 30% of the patients had two or more comorbidities; 10% of patients had poor performance status.

Treatment use

The percentage of advanced NSCLC patients treated with any antineoplastic therapy within two years of diagnosis was 46.7% in 2012 and in 2015 (difference: 0.0%; 95% confidence interval (CI): -1.9, 1.7; Figure 1, Appendix Table 3). Among the patients diagnosed in 2014 and 2015, 7.0% and 15.2% received immune checkpoint inhibitors within two years of diagnosis, respectively. The proportion of patients receiving intravenous targeted therapy remained almost the same, whereas the proportion of patients with oral targeted therapy declined from 9.8% to 8.4% (difference: -1.4%; CI: -2.6, -0.1) between 2012 and 2015.

Among 1324 patients with any immune checkpoint inhibitor claims, 66.5% received platinum doublets with or without bevacizumab only prior to immune checkpoint inhibitor receipt; 25.0% received multiple prior antineoplastic therapies or non-standard regimens. Only 5.2% had no antineoplastic therapy claims prior to immune checkpoint inhibitor receipt.

Survival

Between 2012 and 2015, overall survival for all patients diagnosed with advanced NSCLC improved (Figure 2, Table 2, Appendix Table 4). The one-year survival probability increased by 3.9% (CI: 2.3, 5.5) from 32.0% in 2012 to 35.9% in 2015. The two-year survival probability also increased by 3.3% (CI: 2.0, 4.5). The median survival increased from 6.3 months in 2012 to 6.7 months in 2015 (difference: 0.4 months; CI: 0.0, 0.9). Restricted mean survival time at two years increased from 9.3 months to 9.9 months (difference: 0.6 months; CI: 0.4, 0.9).

Spending

Two-year mean total spending increased from $66848 in 2012 to $72583 in 2015 (difference: $5735; CI: 3479, 8040; Figure 3A, Table 2, Appendix Table 5-6). These changes were mainly due to increased outpatient spending (Figure 3B). Two-year mean outpatient spending increased from $31502 in 2012 to $39163 in 2015 (difference: $7661; CI: 5902, 9311). In contrast, two-year mean acute inpatient spending decreased from $24895 to $23546 (difference: $-1349; CI: -2270, -436) during the same period.

Subgroup analysis by the probability receiving any antineoplastic therapy

In the highest quintile of predicted probability of antineoplastic therapy receipt, 71.3% had at least one claim for antineoplastic therapy within two years of diagnosis; 21.4% had immune checkpoint inhibitor claim in 2015. In the lowest quintile, only 19.2% had any antineoplastic therapy claim; 5.3% had immune checkpoint inhibitor claim in 2015 (Appendix Methods 2).

Patients with higher predicted probability of treatment receipt had greater improvements in survival than those with lower probability (Figure 2, Table 2, Appendix Table 4). In the highest quintile, the one-year and two-year survival probabilities improved by 7.0% (CI: 2.9, 11.7) and 6.2% (CI: 2.1, 10.2) between 2012 and 2015, respectively. Median survival increased by 2.3 months (CI: 1.1, 4.5). In contrast, changes were smaller and not statistically significant for patients in the lowest quintile. Appendix Table 4 describes the detailed survival outcomes in all quintile groups.

Patients in the highest quintile also had a higher increase in total and outpatient spending than those in the lowest quintile; two-year mean total and outpatient spending increased by $9257 (CI: 5120, 18617) and $11437 (CI: 7964, 18066), respectively (Table 2, Appendix Table 5-6). Among patients in the lowest quintile, the change in mean total spending was smaller and not statistically significant (difference: $2692; CI: -1297, 7157). Two-year outpatient spending increased by $3286 (CI: 1525, 5940).

Part D drug spending also increased between 2012 and 2015 among those with Part D enrollment. The differences in two-year mean Part D spending were $3373 (CI: 1890, 4769), $5339 (CI: 2470, 8980), and $814 (CI: -1457, 3153) for all patients, those in the highest quintile, and those in the lowest quintile, respectively.

Descriptive and exploratory analyses

Appendix Table 7 describes the subgroup analysis of patients with at least one antineoplastic therapy claim within two years of diagnosis (n= 12067). Results were similar to the results of patients with higher predicted probability of any antineoplastic therapy. Our findings were also similar when we used specific HCPCS codes only to identify immune checkpoint inhibitors (Appendix Table 8-9).

Among 1324 patients with at least one immune checkpoint inhibitor claim within two years of diagnosis, the mean two-year total and outpatient spending were $159,725 and $121,061, respectively (Appendix Table 10). This analysis is purely descriptive and cannot be interpreted as indicating the effect of treatment with immune checkpoint inhibitors. Some of the spending accrues before inhibitor receipt and patients who survive (and accrue costs) for a longer period may be more likely to receive these therapies.

DISCUSSION

The rapid adoption of immune checkpoint inhibitors was accompanied by considerable increases in overall survival and Medicare spending in older adults diagnosed with advanced NSCLC between 2012 and 2015. The changes were more pronounced among patients who were more likely to receive

antineoplastic therapy, suggesting that changes may be attributable to the introduction of immune checkpoint inhibitors.

Among all older adults diagnosed with advanced NSCLC in 2015, 15.2% received immune checkpoint inhibitors within two years of diagnosis; approximately 32.5% of patients with any antineoplastic therapy received immune checkpoint inhibitors. Immune checkpoint inhibitors were approved only as second-line or later treatment until October 2016. Accordingly, in our study, the majority of patients who received these therapies had received prior antineoplastic therapy. Despite the increasing use of immune checkpoint inhibitors, more than half of older adults continued to receive no antineoplastic therapy, presumably due to limited expectation of benefits and risk of toxicity.[23,24]

The observed improvements in overall survival are likely attributable, at least in part, to the introduction of immune checkpoint inhibitors; patient characteristics and general practice patterns are unlikely to have significantly changed during the same four-year period. Key clinical practice guidelines for systemic chemotherapy and targeted therapy also remained similar during the study period.[25,26] The effectiveness of immune checkpoint inhibitors among older adults has been questioned in some prior studies because of their underrepresentation in the seminal clinical trials and age-related changes in immune function.[3,27-29] The findings of our study suggest that the introduction of these therapies may have improved survival at the population level, especially among those who are likely to be candidates for antineoplastic therapy treatment.[27]

Several prior studies using SEER-Medicare data have examined trends in survival prior to the introduction of immune checkpoint inhibitors.[2,11,30] These studies analyzed the survival trend over a ten-year period, which includes approvals of multiple new therapies and greater variations in practice patterns. In a recent study that used the Flatiron Health database, the median overall survival improved by 2.1 months before and after the approval of immune checkpoint inhibitors among patients who received second-line therapy for NSCLC.[31]

Despite the decrease in acute inpatient spending, from 2012 to 2015, the mean two-year total and outpatient spending substantially increased by $5735 and $7661, respectively. The increase is not surprising in view of increased survival and adoption of immune checkpoint inhibitors, however, the magnitude of the spending increase raises concerns on the financial impact and accessibility of these therapies to the Medicare program and its beneficiaries. Further studies are needed to understand the cost-effectiveness of these therapies.

During our study period, immune checkpoint inhibitors had been approved as either the second-line treatment after disease progression or the first-line treatment for those with high PD-L1 expression. In recent years, more patients with advanced NSCLC are receiving these therapies because of their approval for additional indications.[32,33] For example, pembrolizumab was approved as the first-line treatment for metastatic NSCLC in combination with pemetrexed and carboplatin, regardless of PD-L1 expression, in May 2017.[32] Current data only allow us to study the early impact of the introduction of these therapies in clinical practice. Nevertheless, we were able to detect substantial population-level impacts in overall survival and spending. Future studies can examine whether improvements in survival and increases in spending have continued in recent years.

Our study has some limitations. First, given the lack of detailed clinical information in the SEER-Medicare data (e.g., lack of data on PD-L1 expression, genetic mutation status, disease progression, lines of therapy) we could not directly compare the survival and spending between those who are treated and not treated with immune checkpoint inhibitors or identify those who would be specifically eligible to these treatments. Nevertheless, our population-based analyses provide information on the overall effect of the introduction of these therapies in a general population of older adults with advanced NSCLC. Second, we only examined the early impact of these therapies because currently available SEER-Medicare data do not extend beyond 2015 for cancer diagnosis and 2016 for Medicare claims.

In conclusion, the increasing use of immune checkpoint inhibitors has been accompanied by improvements in overall survival and increases in total Medicare spending in population of older adults

with advanced NSCLC. The survival improvements that we observed during a four-year study period are noteworthy, considering the poor prognosis of advanced NSCLC that has remained relatively unchanged in the past few decades.[2,11] Nevertheless, the magnitude of spending increases raises concerns about the financial burden of the novel treatments. As various new targeted therapies continue to change the treatment of advanced NSCLC, future studies will be needed to understand their clinical benefits and financial impacts.

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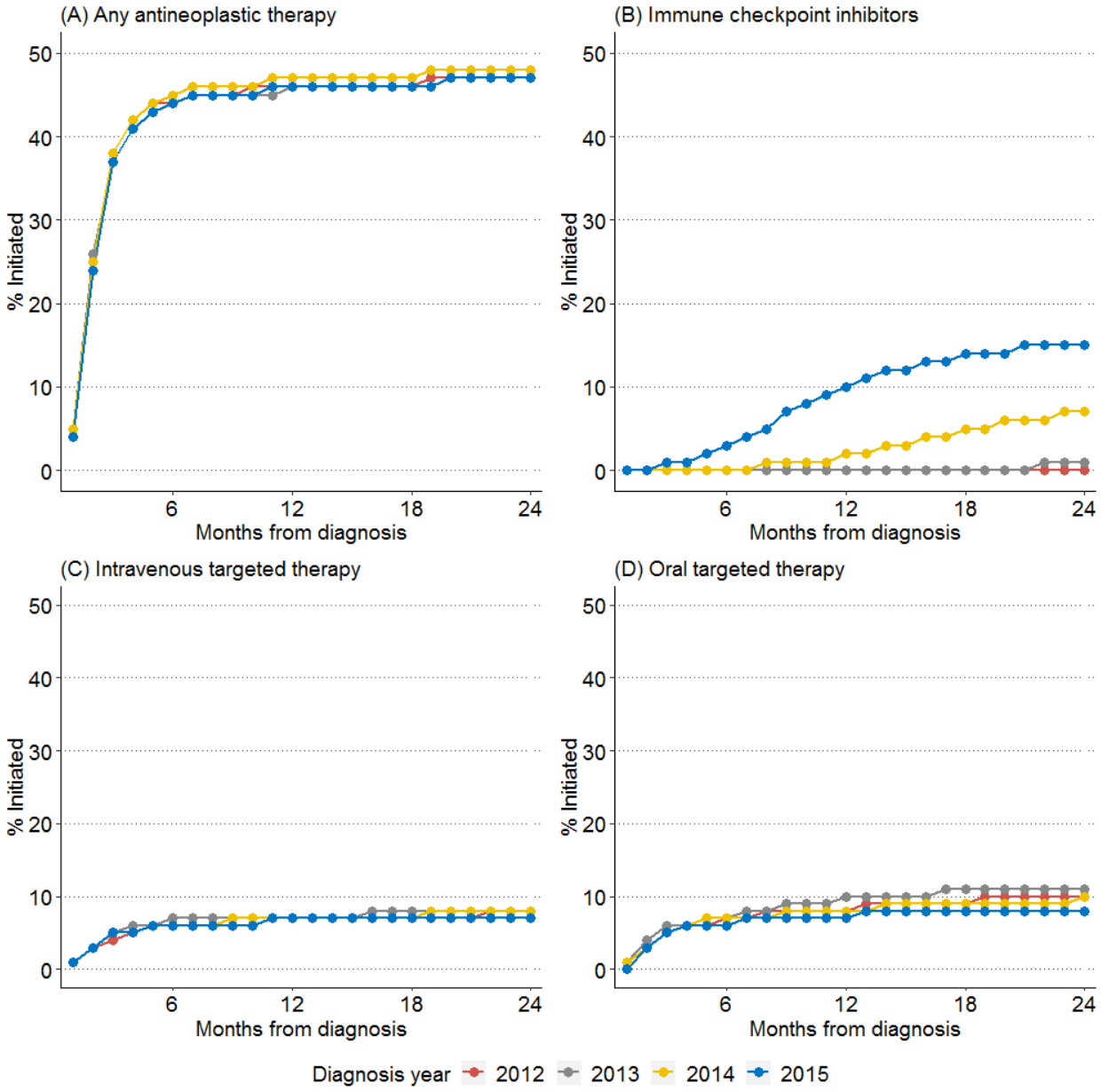
[Table 1] Baseline patient characteristics by year of diagnosis

	Year of diagnosis (%)			
	2012 (n=6725)	**2013** (n=6435)	**2014** (n=6447)	**2015** (n=6234)
Age at diagnosis, years				
65-74	48.4	49.2	48.8	48.2
75-84	40.0	39.1	39.4	39.7
≥85	11.6	11.7	11.8	12.1
Sex				
Female	46.5	47.9	47.6	48.0
Race				
White	83.1	82.7	82.7	82.5
Black	9.2	9.1	9.6	9.5
Asian	3.9	4.2	3.7	3.6
Other	3.8	4.0	4.0	4.4
Stage at diagnosis				
IIIB	13.2	13.4	14.2	13.0
IIIC	23.9	22.9	22.8	23.5
IV	62.9	63.7	63.0	63.5
Histology				
Non-squamous	56.7	57.5	58.3	59.3
Squamous	29.0	29.7	29.6	29.1
NSCLC NOS	14.3	12.8	12.1	11.6
Brain metastasis at diagnosis				
No	82.7	84.0	83.7	83.8
Yes	13.6	13.1	14.0	14.1
Unknown	3.7	2.9	2.3	2.1
Medicare original reason for entitlement				
Age	86.2	85.6	85.6	85.2
Disability/ESRD	13.8	14.4	14.4	14.8
Medicaid dual eligibility[a]				
Yes	19.7	20.4	19.6	18.8
Region				
West	38.3	38.7	39.1	38.1
South	29.3	28.6	28.6	29.0
Midwest	13.3	13.1	12.6	12.9
Northeast	19.2	19.7	19.8	20.0
Number of Charlson comorbid conditions[a]				
0	39.9	39.5	39.2	39.8
1	27.6	27.9	27.2	27.0
≥2	32.4	32.6	33.6	33.2
Proxy of performance status[a]				
ECOG 0-1	90.1	89.4	89.5	89.5
ECOG 2-4	9.9	10.6	10.5	10.5

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESRD, end-stage renal disease; NOS, not otherwise specified; NSCLC, non-small cell lung cancer.

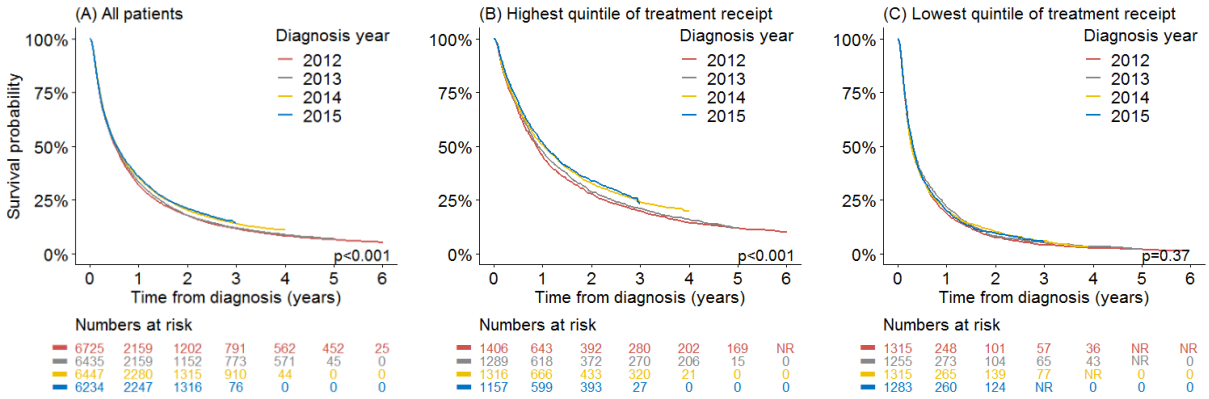
[a] In the year prior to diagnosis.

[Figure 1] Cumulative percentage of treatment receipt by year of diagnosis



[Note] Any antineoplastic therapy includes systemic chemotherapy, immune checkpoint inhibitors, and intravenous targeted therapy that are covered by Medicare Part A and B. Receipt of oral targeted therapy was examined among the subgroup of patients with Medicare Part D coverage.

[Figure 2] Kaplan–Meier survival curves by year of diagnosis

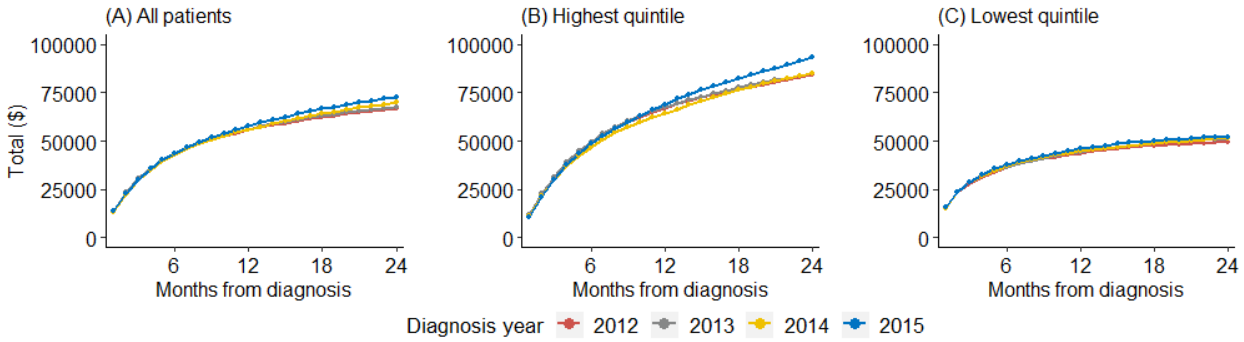


Abbreviations: NR, not reported.

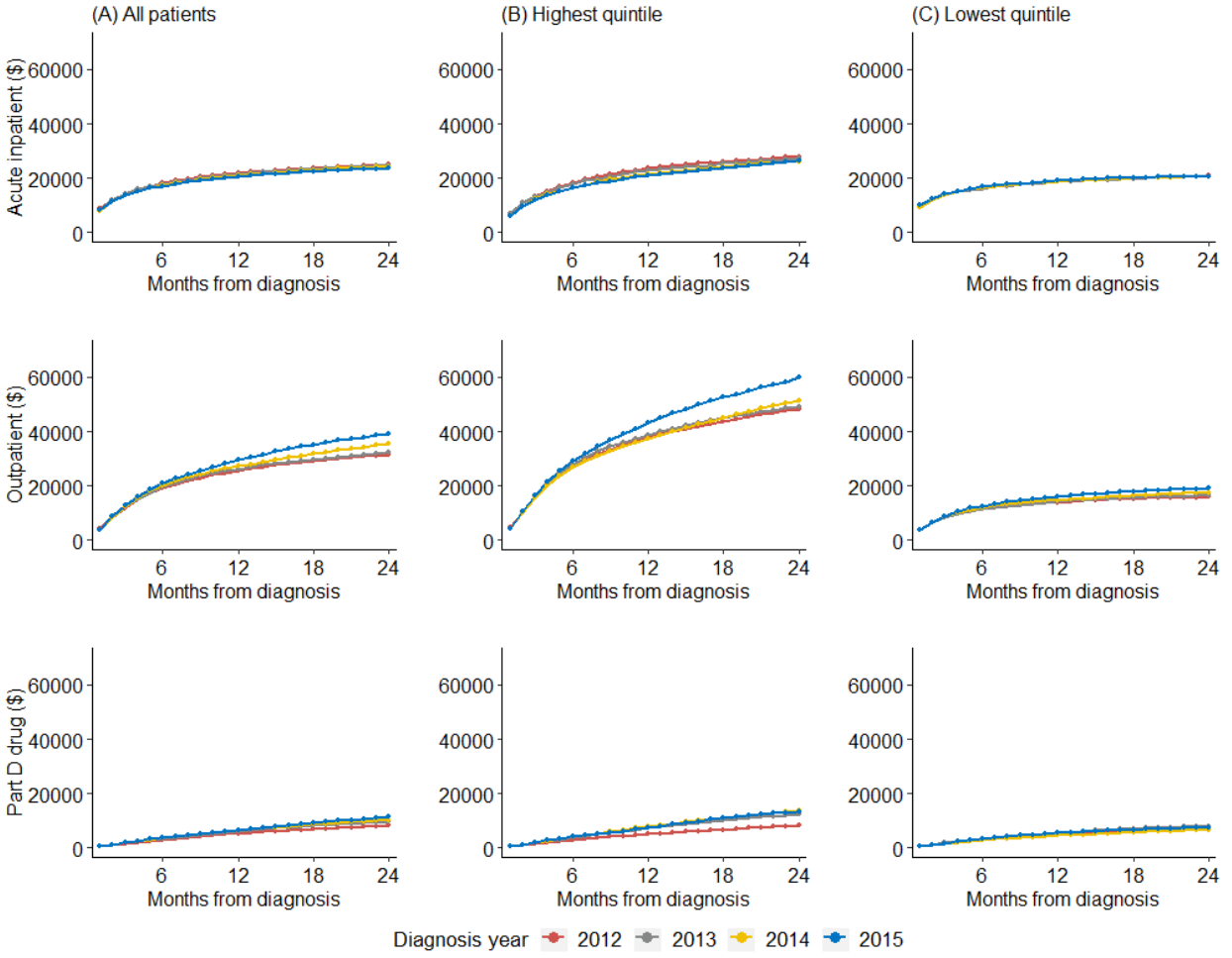
[Note] Overall survival by year of diagnosis among all patients (Panel A, n=25841), patients in the highest quintile of probability of any antineoplastic therapy receipt (Panel B, n=5168), and patients in the lowest quintile of probability of any antineoplastic therapy receipt (Panel C, n=5168). Cell sizes of less than 11 were suppressed per National Cancer Institute rules to preserve patient confidentiality. If a cell size of less than 11 can be extrapolated mathematically, we also suppressed the second smallest cell. P-values are from log-lank tests.

[Figure 3] Cumulative mean spending per patient by year of diagnosis

A. Total Medicare spending



B. By spending category



[Note] Cumulative mean spending per patient compared by year of diagnosis among all patients (first column, n=25841), patients in the highest quintile of probability of any antineoplastic therapy receipt (second column, n=5168), and patients in the lowest quintile of probability of any antineoplastic therapy receipt (third column, n=5168).

[Table 2] Changes in survival and mean spending per patient from 2012 to 2015

	Difference 2015-2012 (95% confidence interval)		
	All patients	**Highest quintile**	**Lowest quintile**
Survival			
One-year survival probability, %	3.9 (2.3, 5.5)	7.0 (2.9, 11.7)	1.8 (-2.0, 4.5)
Two-year survival probability, %	3.3 (2.0, 4.5)	6.2 (2.1, 10.2)	2.6 (-0.1, 4.4)
25% survival, months	0.1 (-0.1, 0.2)	0.6 (-0.1, 1.7)	0.1 (-0.1, 0.3)
Median survival, months	0.4 (0.0, 0.9)	2.3 (1.1, 4.5)	0.2 (-0.3, 0.6)
75% survival, months	3.1 (1.9, 4.2)	Not available[a]	0.9 (-0.7, 2.3)
Restricted mean survival at two years, months	0.6 (0.4, 0.9)	1.2 (0.6, 2.1)	0.4 (-0.3, 0.8)
One-year cumulative mean spending, $			
Total	2108 (616, 3668)	2021 (-419, 7477)	2236 (-786, 5618)
Acute inpatient	-1259 (-2182, -452)	-2573 (-4628, -58)	27 (-2014, 1726)
Outpatient	3772 (2696, 4833)	5255 (3456, 9261)	2076 (964, 3949)
Part-D drug	1332 (637, 2040)	2401 (1100, 4475)	642 (-917, 1770)
Two-year cumulative mean spending, $			
Total	5735 (3479, 8040)	9257 (5120, 18617)	2692 (-1297, 7157)
Acute inpatient	-1349 (-2270, -436)	-1710 (-4092, 1346)	-185 (-2431, 1731)
Outpatient	7661 (5902, 9311)	11437 (7964, 18066)	3286 (1525, 5940)
Part-D drug	3373 (1890, 4769)	5339 (2470, 8980)	814 (-1457, 3153)

[a] 75% survival was not reached for patients diagnosed in 2015.

CHAPTER 2. Real-world use and survival outcomes of immune checkpoint inhibitors in older adults with non-small cell lung cancer

INTRODUCTION

The introduction of immune checkpoint inhibitors has changed the treatment approach to advanced non-small cell lung cancer (NSCLC). In 2015, the US Food and Drug Administration approved the first two programmed cell death protein (PD-1) targeting monoclonal antibodies, nivolumab and pembrolizumab, for patients with advanced NSCLC. In the CheckMate-057 and 017 trials, nivolumab significantly improved overall survival over docetaxel among advanced NSCLC patients with progression on or after platinum-based chemotherapy.[1,2] The median overall survival in patients who received nivolumab were 12.2 months and 9.2 months for those with non-squamous and squamous histology, respectively.[1,2] In the KEYNOTE-010 trial, pembrolizumab improved overall survival by 1.9 months compared with docetaxel among patients with at least 1% PD-L1 expression.[3] The median overall survival in patients with pembrolizumab was 10.4 months.[3]

These seminal clinical trials demonstrated the clinical efficacy of immune checkpoint inhibitors. Little is known, however, about the characteristics and prognosis of older adults receiving these therapies in routine oncology practice because they were underrepresented in the trials.[1-4] Furthermore, patients with poor performance status and autoimmune conditions were excluded from the trials. In this study, we used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database to determine the characteristics and prognosis of older adults with NSCLC treated with immune checkpoint inhibitors in routine oncology practice.

METHODS

Study design and data: We used the SEER-Medicare linked data to identify patients who were diagnosed with pathologically confirmed stage I-IV NSCLC between 2002 and 2015 and were treated with nivolumab or pembrolizumab between 2014 and 2016. We identified nivolumab and pembrolizumab receipt using Healthcare Common Procedure Coding System (HCPCS) and National Drug Codes in Medicare claims. To ensure the completeness of information on treatment initiation, we included patients

who initiated these therapies two or more months after specific HCPCS J codes became available in January 2016 (i.e., J9299 for nivolumab and J9271 for pembrolizumab). Patients with a first immune checkpoint inhibitor claim prior to March 2016 were excluded from survival analyses because they were considered to have potentially incomplete initiation date information (e.g., may have had prior claims with non-specific J codes or temporary billing codes).We only included patients who were continuously eligible for Medicare Parts A and B and were not enrolled in a Medicare Advantage plan from diagnosis to initiation (or at least 12 months prior to initiation, whichever was longer) to identify baseline characteristics and treatment history. We excluded patients under 65 years of age and those with history of non-lung cancer for which immune checkpoint inhibitors are also indicated. We followed patients from treatment initiation through December 31, 2017.

Outcomes and covariates: The outcome was overall survival; covariates included patient and tumor characteristics and treatment history. We obtained information on patient age, sex, race, original reason for Medicare entitlement, Medicaid dual eligibility, rural, region, diagnosis year and month, stage at diagnosis, and histology. We also identified the number of Charlson comorbid conditions,[5-7] a proxy of performance status,[8,9] presence of 31 autoimmune conditions during the year before immune checkpoint inhibitor initiation,[10] and central nervous system (CNS) metastasis within six months prior to initiation from Medicare claims.[11] The proxy of performance status was based on claims for healthcare services commonly used by patients with poor performance status, such as home oxygen, wheelchair, and home health services.[8]

We extracted information on treatment history, including prior systemic and oral targeted therapy, recent radiation therapy, care at National Cancer Institute (NCI)-designated cancer centers, and time from initial diagnosis to immune checkpoint inhibitor initiation. Prior systemic therapy included systemic chemotherapy or infusion targeted therapy since diagnosis, and was classified as none, single agent-chemotherapy, platinum doublets with or without bevacizumab, and other. We assessed prior oral targeted therapy with epidermal growth factor receptor tyrosine kinase (EGFR TKIs), anaplastic lymphoma kinase

(ALK) and ROS1, BRAF and MEK inhibitors. Patients who did not have continuous Part D enrollment from diagnosis and had no oral targeted therapy claims were classified as unknown. We provide the codes and definitions of study variables in eTable 1 in the Supplement.

Statistical analysis: We summarized patient and tumor characteristics and treatment history. We estimated survival curves using the Kaplan-Meier method and identified prognostic factors for death using Cox proportional hazards regression. In exploratory descriptive analyses, we examined subgroups by histology and stage at initial diagnosis. We also examined the proportion and median survival of patients with baseline steroid or other immunosuppressant use by prior autoimmune disease status. To assess the robustness of our findings, we applied different criteria for cohort selection and variable definitions. First, we excluded patients with history of any other cancer prior to immune checkpoint inhibitor initiation and examined whether the findings are similar to the main analyses. Second, we included patients with a first immune checkpoint inhibitor claim prior to March 2016. Third, we used a 1-year covariate assessment period to identify CNS metastasis. We performed analyses using SAS software, version 9.4 (SAS Institute Inc) and R software, version 3.5.2 (R Foundation for Statistical Computing). The Brown University Institutional Review Board waived approval requirement for this study.

RESULTS

Among 4,324 patients who received immune checkpoint inhibitors, 1,256 met the study eligibility criteria (Figure 1; eTable 2 and Table 1 summarize the characteristics of all treated patients and the final cohort of immune checkpoint inhibitor initiators, respectively) Of the 1,256 patients, 1,156 (92.0%) initiated nivolumab and 100 (8.0%) initiated pembrolizumab. The median age at treatment initiation was 75.3 years (interquartile range 8.5) and 8.4% of patients were older than 85 years. Approximately half (48.7%) of the patients had two or more comorbidities; 11.5% had poor performance status on the claims-based proxy variable; and 12.6% had a history of autoimmune conditions. Approximately half of the patients (49.7%) initiated immune checkpoint inhibitors after platinum-doublets; 8.1% had no systemic therapy prior to immune checkpoint inhibitors initiation. Approximately 20% of patients received care at

an NCI-designated cancer center. Median time from diagnosis to initiation were 14.1 and 19.3 months for those initially diagnosed with stage IV and I-III disease, respectively.

Median overall survival from immune checkpoint inhibitor initiation was 9.3 months (95% CI: 8.5-10.5); the one-year survival probability was 43.0% (95% CI: 40.2-45.7) and the 18-month survival probability was 31.3% (95% CI: 28.5-34.1). Survival curves stratified by number of comorbid conditions, histology, and treatment history are shown in Figure 2.

Multiple comorbid conditions, squamous histology, history of non-platinum doublet systemic therapy, recent radiation therapy, and shorter time from initial diagnosis to initiation were statistically significantly associated with increased hazard of death in multivariable survival analyses (Table 1). For example, those who received multiple prior systemic therapies or non-standard regimens had worse survival outcomes than those who received only platinum-doublets prior to immune checkpoint inhibitors. Patient demographics, performance status on the claims-based proxy, prior autoimmune conditions, stage at initial diagnosis, and prior oral targeted therapy were not significantly associated with increased hazard of death.

The results of exploratory analyses stratified by histology and stage at initial diagnosis are described in eTable 3-eTable 6 in the Supplement. The proportions of patients with baseline injection steroid use were 46.8% and 32.0% for those with or without history of autoimmune disease, respectively. The proportions of patients who had received any steroid (injection or oral) or other immunosuppressant are described in eTable 7. Results of median survival stratified by prior autoimmune disease and baseline injection steroid use are described in eTable 8.

Our findings were robust to changes in the criteria for cohort selection and variable definitions. First, the results were similar to the main analyses when we excluded patients with history of any malignancy other than lung cancer prior to treatment initiation (eFigure 1 and eTable 9). Second, the results were also similar when we included patients with a first immune checkpoint inhibitor claim prior

to March 2016 (eFigure 2, eTable 10). The median overall survival after the first claim date was 8.7 months (95% CI: 8.4-9.6). Third, using a 1-year covariate assessment period to identify CNS metastasis did not change the main findings (eTable 11).

DISCUSSION

We used real-world data to examine the characteristics and prognosis of a large cohort of older adults with NSCLC who initiated immune checkpoint inhibitor therapy. Median survival after immune checkpoint inhibitor initiation was 9.3 months. Older adults in our study were likely to have underlying health problems other than NSCLC, including multiple comorbid conditions, prior autoimmune disease, or proxy of poor performance status. The percentage of patients receiving care at NCI-designated cancer centers was higher than the previously reported rate of NCI-cancer center attendance in patients with advanced lung cancer,[12] and it is likely to reflect the earlier adoption of immune checkpoint inhibitors in these centers.

We found that factors that are generally related to poor prognosis among advanced NSCLC patients in routine practice, such as comorbid conditions, squamous histology, failure of aggressive prior treatment or non-standard regimens, or need for (palliative) radiation, remain predictors of poor prognosis in older adults treated with immune checkpoint inhibitors.[13,14] Shorter time from initial diagnosis to immune checkpoint inhibitor initiation was also associated with poor prognosis and possibly identifies patients with rapid disease progression, given that nivolumab and pembrolizumab were mainly used as later lines of treatment during the study period. Similar to prior results from community based cancer clinics,[15] we found no differences in prognosis between different age groups or those who received these therapies as first-line or second-line after platinum-doublets. We also found no difference by prior oral targeted therapy use.

In our multivariable analyses, autoimmune conditions were not associated with the hazard of death. Though it is likely that patients with severe autoimmune disease were not included in our initiator

cohort, our result suggests that autoimmune conditions may not be an absolute contraindication for immune checkpoint inhibitor therapy.[16] Patients with a history of autoimmune conditions were more likely to have received injection steroids at baseline compared to patients without such history, however, our descriptive analyses could not examine the reasons for the use of these medications. Further studies are warranted to determine which patients with autoimmune conditions can be safely treated with immune checkpoint inhibitors.

Our study has several limitations. First, SEER-Medicare data do not have information on genetic mutation status including PD-L1 expression level and smoking status. The majority of patients in our cohort received nivolumab which was approved regardless of PD-L1 expression level, and our analysis reflects the practice patterns during the study period. Second, our results of oral targeted therapy may have been influenced by the lack of information for those without Medicare Part D coverage. Third, due to data availability, our survival analyses were restricted to patients who were diagnosed until December 31, 2015 and initiated immune checkpoint inhibitors between March 1, 2016 and December 31, 2016. Patients included in survival analyses are likely to have longer time from initial diagnosis to immune checkpoint inhibitor initiation than those who were not. Fourth, our claim-based algorithms for identifying selected baseline characteristics, including CNS metastasis and prior autoimmune conditions, may not be completely accurate. We used algorithms based on prior literature for these conditions,[10,11] however the validity of these algorithms has not been fully assessed. We used previously validated algorithms for comorbid conditions and proxy for performance status to reduce missclassification.[6,9] Fifth, SEER-Medicare data are not geographically representative of the U.S. population; patients in the Midwest and Northeast are underrepresented and those in the West and South are overrepresented.[17] The Midwest and South regions have higher smoking, lung cancer incidence, and mortality rate compared to the West and Northeast regions.[18-20] The impact of these sample characteristics on our findings is difficult to fully evaluate, however, we found no difference in survival outcomes with respect to geographic region. Sixth, we could not directly determine the line of therapy from SEER-Medicare data. However, prior systemic

therapy variable in our analysis can be considered a surrogate for the line of therapy as it identifies regimens received prior to immune checkpoint inhibitor initiation. Seventh, our results may not apply to patients under the age of 65 years. That said, our findings were generally similar to a prior study that included younger patients treated with immune checkpoint inhibitors in routine practice.[15] As in our analyses, that study did not find an association between age and survival among patients treated with immune checkpoint inhibitors.

In conclusion, we identified predictors of mortality in older adults with NSCLC receiving immune checkpoint inhibitors in routine practice. Many older adults with NSCLC who initiated immune checkpoint inhibitors in routine oncology practice had multiple comorbidities or history of autoimmune disease. Factors associated with poor prognosis among patients with advanced NSCLC also predicted decreased survival in older adults treated with immune checkpoint inhibitors.

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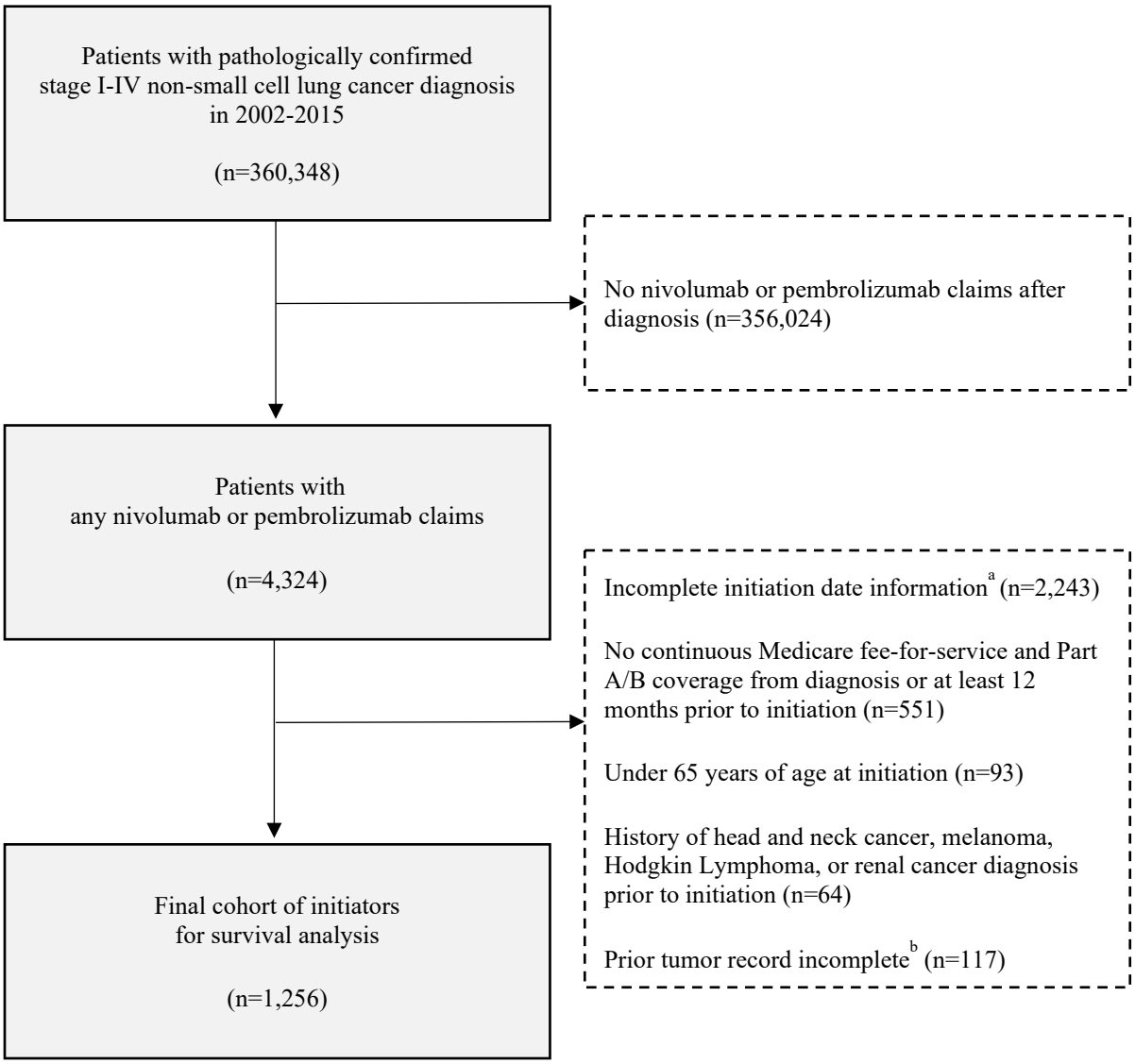
Figure 1. Cohort selection diagram



[a] First immune checkpoint inhibitor claim prior to March 1, 2016. Specific Healthcare Common Procedure Coding System J codes to identify immune checkpoint inhibitors from Medicare claims (i.e., J9299 for nivolumab and J9271 for pembrolizumab) became available in January 2016. We used a two-month wash-out period to ascertain treatment initiation.

[b] Lung cancer was not the first primary malignant cancer, but information on prior disease was unavailable.

Table 1. Baseline characteristics and their association with mortality

Variables	Cohort (n = 1256) No. (%)	Univariable[a] HR	95% CI	p	Multivariable[b] HR	95% CI	p
Patient characteristics							
Age at initiation, years							
65-74	605 (48.17)	ref			ref		
75-84	545 (43.39)	0.98	(0.85, 1.13)	0.52	1.00	(0.86, 1.16)	0.65
≥85	106 (8.44)	0.86	(0.67, 1.11)		0.88	(0.67, 1.16)	
Sex							
Male	653 (51.99)	ref		0.08	ref		0.76
Female	603 (48.01)	0.89	(0.77, 1.01)		0.98	(0.85, 1.13)	
Race							
White	1072 (85.35)	ref			ref		
Black	89 (7.09)	1.24	(0.96, 1.60)	0.32	1.16	(0.89, 1.51)	0.38
Asian	37 (2.95)	1.16	(0.79, 1.70)		1.35	(0.89, 2.05)	
Other	58 (4.62)	0.92	(0.66, 1.30)		0.99	(0.70, 1.41)	
Medicare original reason for entitlement							
Age	1094 (87.10)	ref		0.54	ref		0.90
Disability/ESRD	162 (12.90)	1.06	(0.87, 1.30)		1.01	(0.82, 1.26)	
Medicaid dual eligibility[c]							
No	1071 (85.27)	ref		0.71	ref		0.15
Yes	185 (14.73)	0.96	(0.80, 1.17)		0.85	(0.69, 1.06)	
Rural							
No	1228 (97.77)	ref		0.41	ref		0.27
Yes	28 (2.23)	0.82	(0.51, 1.32)		0.76	(0.46, 1.24)	
Region							
Northeast	307 (24.44)	ref			ref		
Midwest	143 (11.39)	0.97	(0.76, 1.23)	0.07	0.95	(0.74, 1.22)	0.15
South	308 (24.52)	1.19	(0.99, 1.45)		1.19	(0.97, 1.45)	
West	498 (39.65)	0.96	(0.80, 1.14)		0.98	(0.81, 1.17)	
Number of comorbid conditions[d]							
0	253 (20.14)	ref			ref		
1	392 (31.21)	1.21	(0.99, 1.48)	<0.001	1.17	(0.95, 1.43)	0.002
≥2	611 (48.65)	1.43	(1.19, 1.73)		1.40	(1.15, 1.70)	
Proxy of performance status[d]							
ECOG 0-1	1112 (88.54)	ref		0.42	ref		0.40
ECOG 2-4	144 (11.46)	1.09	(0.88, 1.35)		1.10	(0.88, 1.38)	
Prior autoimmune conditions[d]							
No	1098 (87.42)	ref		0.24	ref		0.51
Yes	158 (12.58)	1.13	(0.92, 1.37)		1.07	(0.88, 1.31)	
Tumor characteristics							
Stage at diagnosis							
I	229 (18.23)	ref			ref		
II	75 (5.97)	1.21	(0.88, 1.66)	0.53	1.12	(0.81, 1.55)	0.42
III	417 (33.20)	1.11	(0.91, 1.35)		1.03	(0.83, 1.28)	
IV	535 (42.60)	1.03	(0.85, 1.25)		0.92	(0.74, 1.14)	
Histology							
Non-squamous	793 (63.14)	ref			ref		
Squamous	372 (29.62)	1.24	(1.07, 1.44)	0.01	1.24	(1.05, 1.45)	0.04
NSCLC NOS	91 (7.25)	1.20	(0.93, 1.55)		1.09	(0.84, 1.42)	
Central nervous system metastasis[e]							
No	1056 (84.08)	ref		0.08	ref		0.25
Yes	200 (15.92)	1.17	(0.98, 1.40)		1.12	(0.92, 1.36)	
Treatment history							
Prior systemic therapy[f]							
Platinum doublets	624 (49.68)	ref			ref		
None	102 (8.12)	0.92	(0.71, 1.20)		1.05	(0.79, 1.38)	
Single-agent chemotherapy	46 (3.66)	1.32	(0.93, 1.86)	0.47	1.53	(1.07, 2.20)	0.01
Platinum doublets + bevacizumab	155 (12.34)	1.05	(0.85, 1.30)		1.26	(1.00, 1.59)	
Other	329 (26.19)	1.07	(0.91, 1.26)		1.31	(1.10, 1.56)	
Prior oral targeted therapy[g]							
No	706 (56.21)	ref			ref		
Yes	114 (9.08)	0.87	(0.67, 1.11)	0.47	1.01	(0.77, 1.31)	0.68
Unknown	436 (34.71)	1.02	(0.88, 1.18)		1.07	(0.92, 1.25)	
Recent radiation[h]							
No	1124 (89.49)	ref		0.001	ref		0.001

Yes	132 (10.51)	1.44	(1.17, 1.77)		1.47	(1.18, 1.83)	
Care at NCI-designated cancer center[i]							
No	1017 (80.97)	ref		0.83	ref		0.97
Yes	239 (19.03)	1.02	(0.86, 1.21)		1.00	(0.84, 1.20)	
Time from diagnosis to initiation							
2 - 6 months	46 (3.66)	ref			ref		
6 months - 1 year	319 (25.40)	0.83	(0.58, 1.17)	0.001	0.83	(0.58, 1.18)	<0.001
1 - 3 years	658 (52.39)	0.68	(0.48, 0.95)		0.64	(0.45, 0.91)	
>3 years	233 (18.55)	0.57	(0.40, 0.82)		0.51	(0.35, 0.76)	

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESRD, end-stage renal disease; HR, harzard ratio; NCI, National Cancer Institute; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; p, p-value; ref, reference group.

[a] Results from univariable Cox proportional hazard models. P values were calculated from Wald tests.

[b] Results from a multivariable Cox proportional hazard model with all variables listed in the table. P values were calculated from Wald tests.

[c] Any state buy-in in the year prior to initiation

[d] In the year prior to initiation.

[e] In the 6 months prior to initiation.

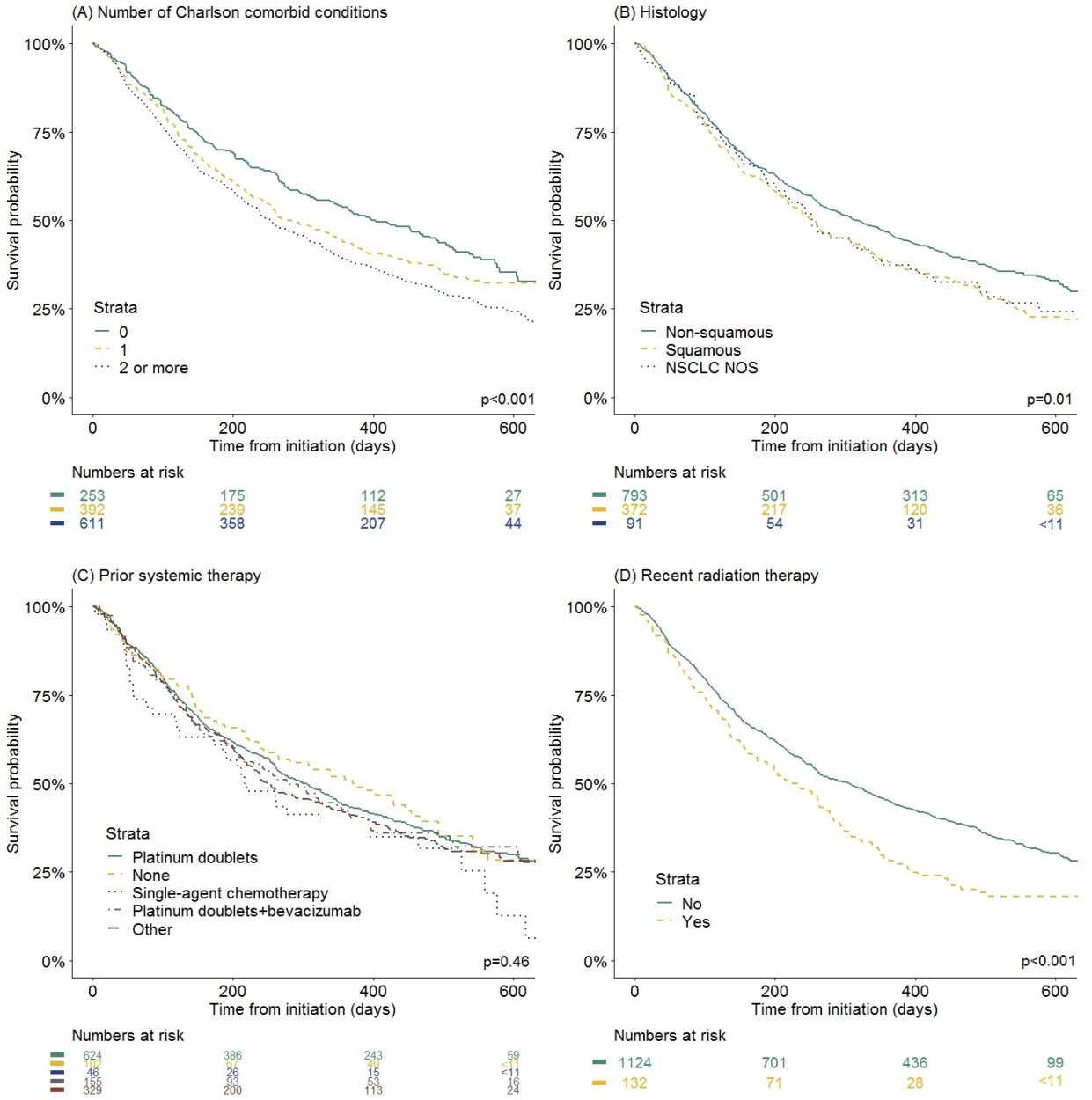
[f] Since diagnosis. Includes chemotherapy and infusion targeted therapy. Excludes oral targeted therapy.

[g] Since diagnosis. Includes epidermal growth factor receptor tyrosine kinase (EGFR TKIs), anaplastic lymphoma kinase (ALK) and ROS1, BRAF and MEK inhibitors. Unknown status for those without continuous Medicare Part D coverage.

[h] In the 30 days prior to initiation.

[i] Defined as having any claim originating at a NCI-designated cancer center in the 90 days prior to initiation.

[Figure 2] Kaplan-Meier survival curves by number of comorbid conditions, histology, and treatment history



Abbreviations: NOS, not otherwise specified; NSCLC, non-small cell lung cancer.

P-values are from log-lank tests. Prior systemic therapy includes chemotherapy and infusion targeted therapy (excludes oral targeted therapy). Recent radiation therapy includes radiation in the 30 days prior to immune checkpoint inhibitor initiation. Cell sizes of less than 11 were suppressed per National Cancer Institute rules to preserve patient confidentiality.

CHAPTER 3. The potential of using SEER-Medicare data to emulate randomized trials: a case study of bevacizumab in advanced breast cancer

INTRODUCTION

Population-based comparative effectiveness studies are increasingly conducted to understand the real-world impact of rapid therapeutic advances in the field of oncology. Despite the potential of these studies to complement the findings of randomized trials and improve evidence-based oncology practice,[1] whether these studies can generate research-grade evidence to inform oncology practice has been questioned by many research methodologists and clinicians.[2,3]

The challenges of observational studies primarily arise from the lack of important clinical variables in routinely-collected databases, as well as the difficulties in study design and analyses to avoid bias and confounding. Key clinical information that guides care for patients with cancer, such as genetic mutation status or disease progression, is often not available in commonly used population-based database, such as the Surveillance, Epidemiology, and End Results (SEER)-Medicare data. Even when this information is available to render treatment groups comparable, observational analyses often become invalid due to common flaws that arise from deviating from the basic principles of study design and analysis.[4,5]

In this study, we determined whether well-designed observational studies using the SEER-Medicare data can correctly infer cancer treatment effects despite the limitations of the database. We conducted a case study of comparative effectiveness of bevacizumab as first-line treatment for patients with human epidermal growth factor receptor 2 (HER2) negative recurrent or metastatic breast cancer. We compared our findings with the results of two randomized controlled trials on the same research question. By conducting a comparative effectiveness study which has common challenges of observational study design and analysis, we aimed to evaluate the role of observational studies in cancer care decision making and to provide a framework to guide the design and conduct of future observational analyses using similar data sources.

METHODS

Data

We used the SEER-Medicare linked data, which provide detailed information about Medicare beneficiaries with cancer. The SEER data contain the demographic and clinical information of incident cancer cases in defined geographic areas that include approximately 30% of the U.S. population. The Medicare data include Medicare enrollment status, survival status, and claims for beneficiaries with fee-for-service coverage. We used Medicare claims from the inpatient, outpatient, physician, durable medical equipment, Part D drug event, home health agency, and hospice files to identify treatment status and study variables. The SEER data on cancer diagnosis were available until December 2013; data on Medicare claims and overall survival status were available until December 2014 and December 2015, respectively.

Emulating a target trial in the SEER-Medicare linked database

To design observational studies that are comparable to the randomized trials, we emulated a hypothetical pragmatic trial of bevacizumab in recurrent or metastatic breast cancer through the analysis of existing SEER-Medicare data. In the target trial framework, the design and conduct of observational analyses for comparative effectiveness research is guided by a hypothetical pragmatic trial that would address the same research question. This framework helps researchers impose structure on routinely-collected large databases, avoid common study design flaws such as immortal person-time bias, and conduct studies that have a causal interpretation despite the compromises needed for analyzing observational data.[6,7] Following this framework, we specified the key components of the protocol of the hypothetical target trial in Table 1. We developed our study criteria based on the protocol of two existing phase 3 randomized trials of bevacizumab to compare the study findings.[8,9]

Patient eligibility criteria

We identified female patients aged 65 years or older who were diagnosed with pathologically confirmed HER2 negative adenocarcinoma of the breast between 2002 and 2011 and initiated first-line

chemotherapy with taxanes or fluoropyrimidines between 2007 and 2011 for locally recurrent or metastatic disease. To identify baseline characteristics and prior treatment history, we included those who were continuously enrolled in Medicare Part A and B fee-for-service from diagnosis or at least 12 months prior to chemotherapy initiation. Other exclusion criteria includes recent use of chemotherapy, vascular endothelial growth factor pathway targeted therapy, hormonal therapy, and surgical procedure, as well as history of other primary malignant tumor, central nervous system (CNS) metastasis, and contraindications to bevacizumab (i.e., thrombosis, cardiac disease, stroke, hemorrhage, hemoptysis, or GI perforation) based on the criteria of the existing phase 3 randomized trials (See Table 1 for details). We also excluded those who entered Medicare due to disability or end-stage renal disease.

Several variables required to operationalize important eligibility criteria, including recurrence status, HER2 status for patients diagnosed prior to 2010, and CNS metastasis after initial diagnosis, are not readily available in the SEER-Medicare data. We therefore used the information available in Medicare claims to create proxies of these variables based on prior literature.[10-12] First, to select patients who initiated first-line treatment for recurrent disease, we identified those who had received initial breast conserving surgery or mastectomy for stage I-III cancer, had a treatment-free interval of at least 90 days, and re-initiated chemotherapy.[10,11] Second, we used the absence of trastuzumab claims as a proxy for HER2 negative status for patients diagnosed in 2002-2009. Patients with HER2 positive advanced breast cancer were recommended to initiate trastuzumab for systemic treatment since early 2000s.[13] To determine the feasibility of our approach, we examined the percentage of HER2 positive patients diagnosed after 2010 who had not received trastuzumab but received other chemotherapies (Appendix Methods 1).[12] Third, we used ICD diagnosis codes to identify CNS metastasis that developed after initial diagnosis.[14] The details of patient eligibility criteria are described in the Appendix Methods 1.

Treatment strategies

We compared the following two strategies: 1. Initiation of bevacizumab at any dose within 2 weeks of initiation of either taxane (docetaxel, paclitaxel) or fluoropyrimidine (capecitabine, fluorouracil)

monotherapy. 2. No initiation of bevacizumab during the same period. We used the 2 week grace period to identify first-line chemotherapy regimen. Given the low sensitivity of capecitabine in Medicare data and the use of bevacizumab as a combination with chemotherapies,[15] patients who initiated bevacizumab only without accompanying chemotherapy were assumed to have initiated the treatment with capecitabine. We performed sensitivity analysis for this assumption as described below.

Primary outcome and follow-up periods

Our primary study outcome was overall survival. We did not examine progression-free survival as in the existing randomized trial because this cannot be accurately identified from the SEER-Medicare database. We followed patients from the date of taxanes or fluoropyrimidine initiation (baseline or time zero) to the earliest of death, censoring event, or maximum follow-up of 156 weeks. Censoring events included (1) the end of survival data on December 31, 2015 (administrative end of follow-up), (2) the end of Medicare claims data during the 2 week grace period (i.e. losing Medicare Part A or B coverage, enrollment in a Medicare advantage plan, or the end of Medicare claims data on December 31, 2014), or (3) initiation of other chemotherapy prior to bevacizumab initiation during the grace period. We also censored individuals who developed contraindications for bevacizumab during the grace period if and when they initiated bevacizumab during the same period.

Statistical analysis plan

When estimating treatment effects with a grace period, an individual cannot be assigned to a treatment strategy at baseline. We therefore created a data set with two copies (clones) of each eligible individual at baseline and assigned each of the clones to one of the treatment strategies. This approach avoids the inclusion of immortal person-time bias due to identifying bevacizumab initiation among those who survive during the 2 week grace period, allows the estimation of absolute risks, and incorporates adjustments for time varying confounders during the grace period.[16] We artificially censored one of the clones when they deviated from the assigned treatment; clones assigned to the bevacizumab treatment

group were artificially censored at 2 weeks if they had not initiated bevacizumab by then. Clones assigned to the no-bevacizumab group were censored if and when they initiated bevacizumab during the 2 week grace period.

We estimated pooled logistic regression models for overall survival using follow-up time (linear and quadratic term in 1 week intervals) and the following baseline covariates: age at initiation, race, state, urban/rural, marital status, Medicaid dual eligibility, area-level poverty level, stage at diagnosis, grade at diagnosis, hormone receptor status, prior cancer therapy since diagnosis (i.e., surgery, radiation, and adjuvant chemotherapy), and chemotherapy regimen (i.e., fluoropyrimidine or taxanes). We also included the number of Chalrson comorbid conditions,[17] a proxy of performance status,[18,19] and flu vaccination during the year before treatment initiation, as well as care at National Cancer Institute (NCI)-designated cancer centers, number of emergency room (ER) visits, and number of hospital admissions during the six month before initiation. We then used the model's predicted values to estimate the absolute 1-year risk difference and survival curves, which were standardized to the baseline covariates. We also obtained average hazard ratio with treatment as the only covariate using pooled logistic regression in the cloned data.

Because artificial censoring in cloned data can introduce potential selection bias, we used inverse probability of censoring weights methods.[16,20] In the original (un-cloned) data, we estimated pooled logistic regression models for bevacizumab initiation during the grace period that included follow-up time, baseline covariates, and the following post-baseline (time-varying) covariates: NCI cancer center use and presence of ER visits in the previous week. Using the predicted values, we estimated the stabilized censoring weights in the cloned data. We used these weights in the models for survival analysis. We considered other censoring events (e.g., end of study follow-up, end of Medicare data, initiation of other chemotherapy) as random. We described the detailed methods of outcome regression and inverse probability of censoring methods in Appendix Methods 2 and provided the codes to define study variables in Appendix Table 1.

We used a nonparametric bootstrap with 500 samples to compute the 95% confidence intervals (CIs) for absolute risks, risk differences, and hazard ratios. All analyses were conducted using SAS software, version 9.4 (SAS Institute Inc).

Sensitivity analyses

To test the robustness of our estimates to different choices of study design and analyses methods, we only included patients who received taxane as their standard chemotherapy and excluded those who received fluoropyrimidines.

RESULTS

We identified 649 patients who initiated first-line treatment of either taxanes or fluoropyrimidines for recurrent or metastatic breast cancer between 2007 and 2011 and met the study eligibility criteria (Figure 1). Table 2 describes patient characteristics at baseline. Of the 649 patients, 511 and 116 patients remained in the taxanes/fluoropyrimidine only group and in the bevacizumab treated group, respectively, after the two week grace period. Compared to the participants in the original randomized trials, those in our study were substantially older and less likely to have received prior cancer therapy (Appendix Table 2).

The estimated 1-year survival was 57.3% (95% confidence interval (CI): 53.4, 61.2) for taxanes or fluoropyrimidine only group and 60.0% (CI: 51.8, 69.4) for bevacizumab treated group (Figure 2, Table 3). The 1-year risk difference was 2.7% (CI: -6.0, 12.8). The average hazard ratio for overall survival was 0.98 (CI: 0.78, 1.19). Our findings were similar to the findings of previous randomized trials, which found no significant overall survival benefits of bevacizumab (Table 3). The results of sensitivity analyses excluding those who received fluoropyrimidine were similar to the main analyses and are described in detail in Appendix Figure 1.

DISCUSSION

We conducted an observational analysis using the SEER-Medicare database and emulated a target trial examining the effectiveness of bevacizumab in recurrent or metastatic breast cancer. Our findings were consistent with the findings of randomized trials, suggesting that well-designed observational studies can correctly infer cancer care treatment effects despite the compromises of observational data analyses.

The role of observational studies in cancer care decision making has largely been limited by the concerns on the validity of study findings[1] A recent review of studies based on the SEER, SEER-Medicare, or the National Cancer Database found no agreement beyond what is expected by chance between the findings of observational analyses and corresponding randomized trials.[2] Observational studies and randomized trials can produce different results not only because of the failure to control for confounding or bias in either studies but also the differences in patient population, practice patterns, and study design choices.[1] It is therefore important to identify the source of discrepancies when such conflicts exist.[1]

The potential use of observational studies in cancer care decision making will continue to depend on the quality of observational analysis. To improve the validity of observational analysis and enhance the interpretation of study findings, researchers can utilize the target trial framework and explicitly emulate a trial. Specifying the protocol of target trial can reduce the risk of common study design flaws in observational analyses (e.g., misalignment of the start of follow-up, eligibility criteria specification, and treatment assignment), guide the use of appropriate statistical methods, and help clarify the key components of research question to improve their applications in clinical practice.[4,21] It can also help identify the source of differences when findings from observational analyses disagree with those of randomized trials.

In addition, the quality of observational data should be continuously improved to enhance their utility in cancer research. Although we were able to use information available in Medicare claims to operationalize several important patient eligibility criteria, including the first-line treatment for recurrent

disease and HER2 negative status, our approach is only feasible when the eligible study population excludes patients without any systemic cancer therapies.[10-12] In addition, we were unable to examine progression-free survival because of the lack of reasonable methods to identify disease progression in the SEER-Medicare data. Without such information in the database, research questions that can be examined without intractable bias or confounding based on the SEER-Medicare data will continue to be limited.

Our study has limitations. The sample size of our analysis was relatively small, which is likely to have been influenced by the age differences in the SEER-Medicare population and the trial participants. Many older females with recurrent or metastatic breast cancer in routine practice do not receive any systemic treatments.[10] We were also unable to examine those who receive anthracycline as their standard chemotherapy because of the small number of older females using this regimen.

In conclusion, the treatment effect estimates using the SEER-Medicare data were similar to the findings of randomized trials. Our findings suggest that well-designed and rigorously conducted observational studies can play a role in cancer care decision making despite the limitations of observational analyses. The target trial framework used in this study can be applied to enhance the validity and applicability of future observational analyses.

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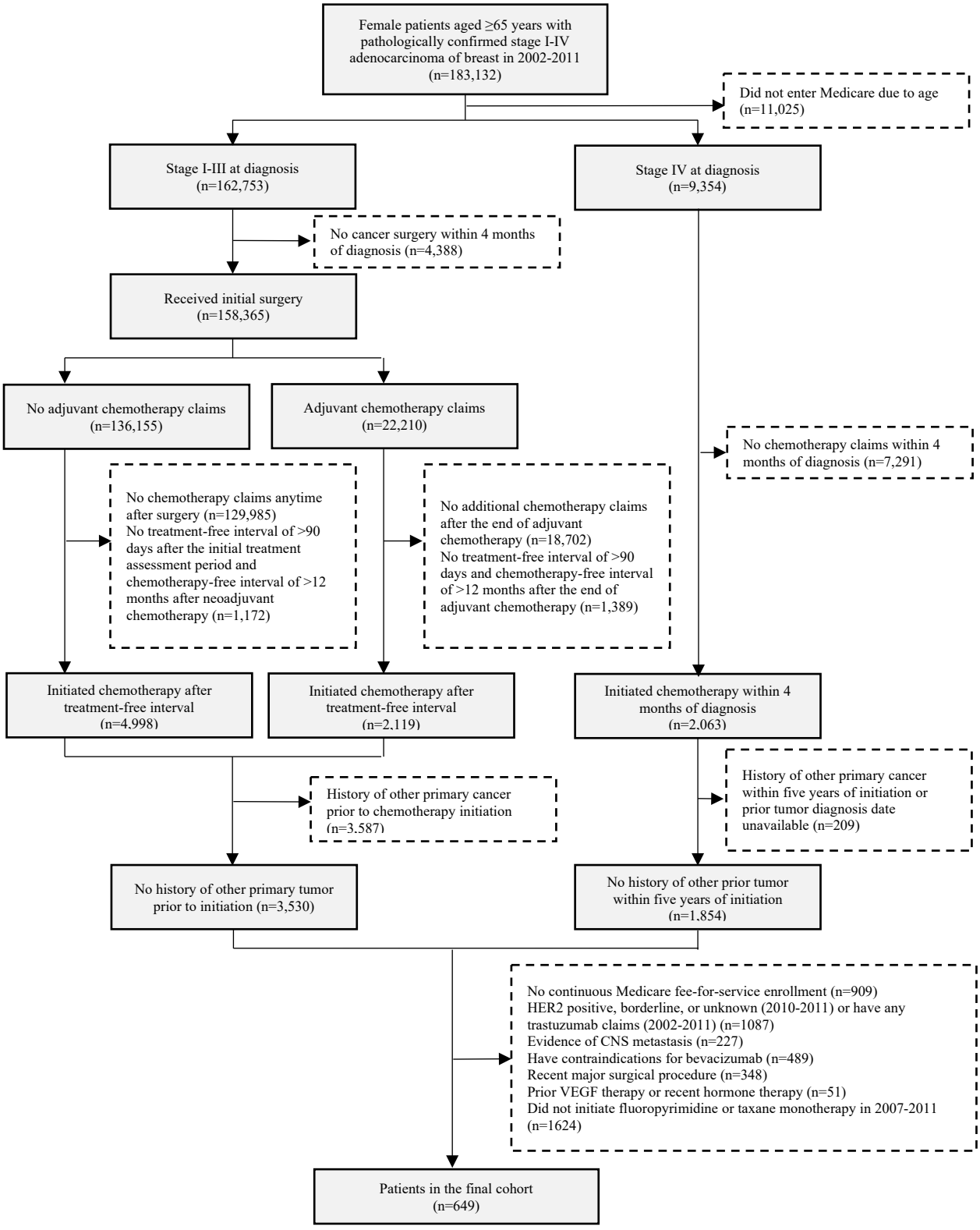
[Table 1] Summary of target trial protocol

Protocol Component	Description of a hypothetical target trial
Eligibility Criteria	• Female patients aged 65 years or older with pathologically confirmed Human Epidermal Growth Factor Receptor 2 (HER2) negative adenocarcinoma of the breast diagnosed between 2002 and 2011 • Initiate first-line chemotherapy (taxanes, fluoropyrimidines) between 2007 and 2011 for locally recurrent or metastatic disease • Enter Medicare due to age • Continuously enrolled in Medicare fee-for-service (Part A and B) from diagnosis or at least 12 months prior to Day 0 • Exclusions – Prior adjuvant or neoadjuvant chemotherapy within 12 months prior to Day 0 – History of other primary malignant tumor (allow patients with history of primary tumor >5 years for those with metastatic disease at diagnosis) – Central nervous system metastasis – Prior therapy with vascular endothelial growth factor pathway-targeted therapy – Prior hormonal therapy less than 1 week prior to Day 0 – Prior invasive therapeutic surgical procedure within 28 days prior to Day 0 – Contraindications to bevacizumab
Treatment Strategies	• Group 1. Initiate taxanes or fluoropyrimidines • Group 2. Initiate taxanes or fluoropyrimidines with bevacizumab
Assignment Procedures	• Unblinded random assignment into treatment strategies. Randomization is assumed conditional on the following covariates: age, race, state, urban/rural, marital status, Medicaid dual eligibility, area-level poverty level, comorbid conditions, performance status, stage at diagnosis, grade at diagnosis, hormone receptor status, prior cancer therapy (surgery, radiation, chemotherapy), flu vaccination, care at National Cancer Institute-designated cancer centers, number of hospital admissions, and number of emergency room visits.
Follow-up period	• Starts at the date of taxane or fluoropyrimidine initiation; ends at death, censoring event, or maximum follow-up of 156 weeks. Censoring event includes (1) the end of survival data on December 31, 2015 or (2) the end of Medicare claims or initiation of other chemotherapy during the grace period.
Outcome	• Overall survival
Causal Contrasts	• Intention to treat effect (i.e., the effect of assignment to treatment at baseline)
Analysis Plan	• Estimate 1-year risks and risk differences using the Kaplan-Meier method; estimate the average hazard ratio using pooled logistic regression model.

[Figure 1] Cohort selection diagram



Abbreviations: CNS, central nervous system; HER2, human epidermal growth factor receptor 2; VEGF, vascular endothelial growth factor.

[Table 2] Characteristics of patients at baseline and the end of the grace period (2 weeks post-baseline)

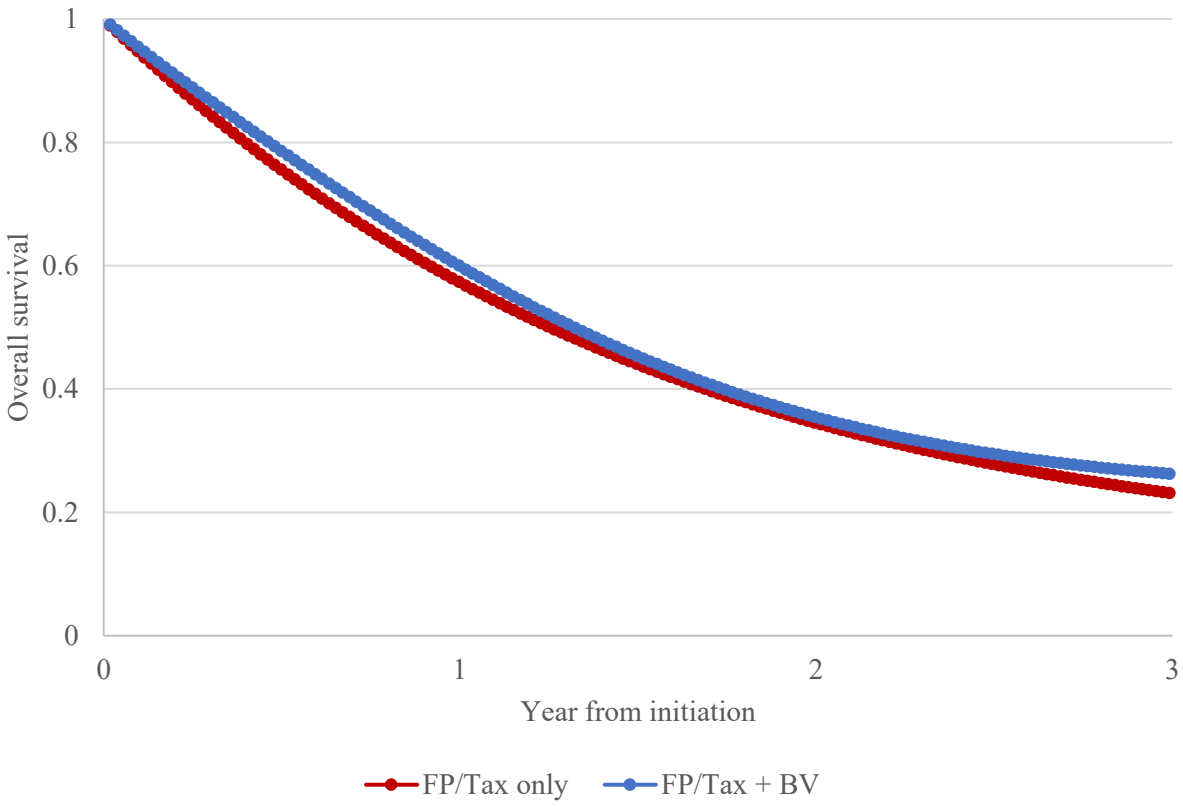
	Baseline All patients (n=649)	2 weeks FP/Tax only (n=511)	2 weeks FP/Tax + BV (n=116)
Age in years, median (range)	77 (66-96)	77 (66-96)	75 (67-91)
Race, %			
White	84.6	84.2	85.3
Black	8.3	8.8	NR
Other	7.1	7.1	NR
State, %			
California	31.3	32.9	21.6
New Jersey	17.0	17.4	17.2
Georgia	12.6	10.2	23.3
Kentucky	7.2	7.6	NR
Lousiana	6.2	5.7	NR
Connecticut	5.6	5.7	NR
Michigan	5.1	5.7	NR
Washington	5.1	5.3	NR
Iowa	4.6	3.9	NR
Utah	2.5	2.7	NR
New Mexico	NR	NR	NR
Hawaii	NR	NR	NR
Rural residence, %			
Less urban or rural	10.8	10.0	14.7
Marital status, %			
Married	47.8	46.2	55.2
Widowed	33.3	33.9	30.2
Other	19.0	20.0	14.7
Medicaid dual eligibility, %			
Yes	14.2	15.1	NR
Area-level poverty, %			
0 to <5%	28.2	27.8	32.8
5 to <10%	27.1	27.6	22.4
10 to <20%	28.7	28.6	27.6
20% to 100% or unknown	16.0	16.1	17.2
# comorbid conditions, %			
0	55.8	54.0	62.9
1	27.7	29.2	23.3
2	9.4	9.6	NR
3≤	7.1	7.2	NR
Poor performance status, %			
Yes	8.8	9.2	NR
Stage at initial diagnosis, %			
I	15.7	15.9	18.1
II	35.8	35.4	35.3
III	22.8	22.5	23.3
IV	25.7	26.2	23.3
Grade at initial diagnosis, %			

Grade I-II	44.8	44.8	NR
Grade III-IV	45.2	44.8	47.4
Not determined	10.0	10.4	NR
Estrogen-Receptor status, %			
Positive	63.2	62.8	62.9
Progesterone-Receptor status, %			
Positive	45.2	44.4	46.6
Prior surgery, %			
None	23.0	24.1	18.1
Breast conserving surgery	30.1	30.3	30.2
Mastectomy	47.0	45.6	51.7
Prior adjuvant chemotherapy, %			
Yes	35.8	35.6	35.3
Prior radiotherapy, %			
Yes	55.9	56.0	56.0
Chemotherapy regimen, %			
Fluoropyrimidines	40.1	45.4	13.8
Taxanes	59.9	54.6	86.2
Flu vaccination, %			
Yes	52.7	52.1	55.2
Care at NCI-designated cancer center, %			
Yes	10.9	12.1	NR
# hospital admissions, %			
0	74.6	75.5	69.8
1	21.9	20.9	NR
2≤	3.5	3.5	NR
# of emergency room visits, %			
0	67.3	67.7	69.0
1	23.1	22.3	NR
2≤	9.6	10.0	NR

Abbreviations: BV, bevacizumab; FP, fluoropyrimidines; NCI, national cancer institute; NR, not reported; Tax, taxanes.

[Note] Cell sizes of less than 11 were suppressed per NCI rules to preserve patient confidentiality. If a cell size of less than 11 can be extrapolated mathematically, we also suppressed the second smallest cell.

[Figure 2] Survival curves from the emulated target trial



Abbreviations: BV, bevacizumab; FP, fluoropyrimidines; Tax, taxanes.

[Table 3] Comparison of overall survival in SEER-Medicare analysis and randomized trials

	SEER-Medicare analysis		AVADO			RIBOON-1			
	FP/Tax only	FP/Tax + BV	Docetaxel + PL	Docetaxel + BV low dose	Docetaxel + BV high dose	Cape + PL	Cape + BV	Tax/Anthra + PL	Tax/Anthra + BV
1-year survival, %	57.3	60.0	76	81	84	74.4	81.0	83.2	80.7
RD* (95% CI)	-	2.7 (-6.0, 12.8)	-	-	-	-	-	-	-
p-value*	-	-	-	0.2	0.02	-	0.08	-	0.4
HR* (95% CI)		0.98 (0.78, 1.19)	-	1.05 (0.81, 1.36)	1.03 (0.70, 1.33)	-	0.85 (0.63, 1.14)	-	1.03 (0.77, 1.38)

Abbreviations: Anthra, anthracycline; BV, bevacizumab; Cape, capecitabine; CI, confidence interval; FP, fluoropyrimidines; HR, hazard ratio; PL, placebo; RD, risk difference; Tax, taxanes.

*Compared to FP/Tax only group (SEER-Medicare analysis) and placebo group (AVADO and RIBOON trial).

Chapter 1 Appendix

[Appendix Table 1] Code definitions for study variables

Variables	Codes
Immune checkpoint inhibitors	
Nivolumab	HCPCS: C9453, J9299 (C9399 and J9999 in 2015 claims) NDC: 00003377412, 00003377211, 00003373413 combined with HCPCS C9399, J3490, J3590, J9999, 96413
Pembrolizumab	HCPCS: C9027, J9271 (C9399 and J9999 in 2015 claims) NDC: 00006302602, 00006302902 combined with HCPCS C9399
Other antineoplastic therapy	
Cisplatin	HCPCS: J9062, J9060, C9418
Carboplatin	HCPCS: J9045
Paclitaxel	HCPCS: J9264, J9265, J9267, C9127, C9431
Docetaxel	HCPCS: J9170, J9171
Vinorelbine	HCPCS: J9390, C9440
Gemcitabine	HCPCS: J9201
Etoposide	HCPCS: J9181, J9182, J8560, C9414, C9425 NDC: 00378326694
Pemetrexed	HCPCS: J9305, C9213
Capecitabine	HCPCS: J8520, J8521 NDC: 51407009612, 69097094808, 69539002092, 69539002099, 69539001960, 69539001999, 51407009560, 51079051005, 42291016712, 72205000660, 16714046701, 16714046801, 00179014970, 00179019570, 00179022970, 00378251191, 00378251278, 67877045812, 67877045830, 67877045860, 60687014994, 69097094903, 65162084306, 65162084406, 65162084416, 65162084450, 50268015413, 42291016660, 59651020508, 59651020510, 59651020410, 72205000792, 59651020460, 00054027121, 00054027223, 16729007212, 16729007329, 67877045912, 67877045930, 67877045960, 63759030001, 63759030011, 64980027606, 64980027712, 00093747306, 00093747489, 00004110020, 00004110150, 00004110116, 00004110051, 00004110013, 00004110022, 00004110113, 00004110151, 00004110175
Other	HCPCS: J9000-J9999, C1166, C1167, C1178, C8953, C8954, C8955, C9127, C9205, C9213, C9214, C9215, C9217, C9218, C9235, C9257, C9262, C9414, C9415, C9417, C9418, C9419, C9420, C9421, C9422, C9423, C9424, C9425, C9426, C9427, C9429, C9431, C9432, C9433, C9437, C9440, G0355, G0356, G0359, G0361, G0370, Q0083, Q0084, Q0085, Q2017, Q2024, Q2049, S0087, S0088, S0115, S0116, S0172, S0176, S0178, S0182, S5019, S5020, S9329, S9330, S9331, J0594, J0894, J7150, J8510, J8520, J8521, J8530, J8560, J8565, J8600, J8610, J8700, J8705, J8999 CPT: 96400-96450, 96530-96549
Intravenous targeted therapy	
Bevacizumab	HCPCS: J9035, S0116, Q2024, C9257, C9214 Excluded ophthalmic use based on the following CPT and principal diagnosis codes CPT: 67028 ICD-9-CM: 362, 361, 365, 379, 25050, 25051, 25052, 25000 ICD-10-CM: H,E11351, E11331, E11341, E11311, E10351, E11359, E10331, E10341, E11329, E10359, E10321, E10311, E11339, E1139, E11349, E11319, E10329, E1039, E13321, E13351, E10339, E13359, E10349, E13341, E13349, E11351
Ramucirumab	HCPCS: C9025, J9308
Necitumumab	HCPCS: C9475
Cetuximab	HCPCS: J9055

Oral targeted therapy[a]	
Erlotinib	NDC: 54868529000, 54868544700, 54868547400, 50242006201, 50242006301, 50242006401
Afatinib	NDC: 00597013895, 00597013790, 00597013730, 00597013830, 00597014130
Gefitinib	NDC: 00310048230, 00310048293
Osimertinib	NDC: 00310134930, 00310135030
Crizotinib	NDC: 00069814020, 00069814120
Ceritinib	NDC: 00078064070
Dabrafenib	NDC: 00078068166, 00173084608, 00173084708
Trametinib	NDC: 00078066615, 00078066815, 00173084813, 00173084913
Alectinib	NDC: 50242013001, 50242013086
Comorbid conditions[b]	
Charlson comorbidities	ICD-9-CM codes and ICD-10-CM codes for Deyo-adapted Charlson comorbidities developed by Quan et al.[1,2] Excluded codes for any malignancy and metastatic solid tumor.
Health service use[c]	
Emergency room visit	Revenue center codes: 0450-0459, 0981 Emergency room charge amount variable in MedPAR file
Annual wellness visit	HCPCS: G0438, G0439
Flu vaccination	HCPCS: G0008, Q2034-Q2039 CPT: 90630, 90682, 90724, 90756, 90653-90662, 90672-90674, 90685-90688

Abbreviations: CM, clinical modification; CPT, current procedural terminology; GNN, generic name variable; HCPCS, healthcare common procedure coding system; ICD, international classification of diseases; NDC, national drug code.

[a] Generic name variable (GNN) was also used.

[b] The presence of each comorbid condition was determined by respective diagnosis codes in one or more inpatient claims or two or more outpatient/physician claims at least 30 days apart. Used all diagnosis codes available during the year prior to diagnosis.

[c] During the year prior to diagnosis.

[Appendix Methods 1] Inverse probability of censoring weighting methods

We accounted for right censoring using the partitioned inverse probability of censoring weighted estimator when estimating the proportion of treatment receipt and mean Medicare spending during the two years of diagnosis.[3] The weights were estimated by using pooled logistic regression models for (1) censoring due to administrative end-of-follow-up and (2) censoring due to changes in Medicare enrollment status. We used the product of the two predicted probabilities from the two regression models to estimate the joint probability of not being censored.

For administrative censoring, we estimated the probability of not being censored using months since diagnosis (t) as the only predictor. During the two-year follow-up, only patients who were diagnosed in 2015 were administratively censored on December 31, 2016. We therefore assigned a probability of one to all observations from patients diagnosed between 2012 and 2014 and also to the $t<14$ observations from those diagnosed in 2015.

For Medicare enrollment censoring (i.e., losing Part A/B enrollment or enrollment in a Medicare Advantage plan), we estimated the probability of not being censored at each month using the following predictors: months since diagnosis (t), square of the months since diagnosis (t^2), age, sex, race, Medicare original reason for entitlement, Medicaid dual eligibility, region, area-level poverty, marital status, year of diagnosis, and cumulative Medicare spending from diagnosis until the previous month ($t-1$). For Part D subgroup analyses, patients were censored for Medicare enrollment status when they lose Part D coverage.

[Appendix Methods 2] Prediction models for the probability of any antineoplastic therapy receipt

To classify patients based on their predicted probability of any antineoplastic therapy receipt, we randomly divided patients into two groups and fitted pooled logistic regression models for any antineoplastic therapy receipt using baseline characteristics.[4] The model results are described in the following Table 1.

[Appendix Method 2 – Table 1] Prediction models for any antineoplastic therapy receipt

	Model from Group 1			Model from Group 2		
Parameter	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value
Intercept	-18.61	2.35	<0.001	-25.52	2.44	<0.001
Months from diagnosis (Ref=24)						
1	2.24	0.44	<0.001	2.02	0.40	<0.001
2	4.11	0.44	<0.001	3.85	0.40	<0.001
3	4.16	0.44	<0.001	3.85	0.40	<0.001
4	3.46	0.44	<0.001	3.06	0.40	<0.001
5	2.92	0.44	<0.001	2.57	0.41	<0.001
6	2.32	0.45	<0.001	2.09	0.41	<0.001
7	1.56	0.46	0.001	1.58	0.42	<0.001
8	1.67	0.46	<0.001	1.25	0.43	0.004
9	1.11	0.48	0.02	0.71	0.45	0.12
10	1.17	0.48	0.02	0.74	0.46	0.11
11	0.99	0.49	0.04	1.01	0.45	0.02
12	1.06	0.49	0.03	0.94	0.45	0.04
13	1.30	0.49	0.01	1.09	0.45	0.02
14	1.21	0.49	0.01	0.43	0.50	0.39
15	0.95	0.51	0.06	0.74	0.48	0.12
16	0.79	0.53	0.13	0.70	0.48	0.15
17	0.64	0.55	0.24	0.51	0.50	0.31
18	0.74	0.54	0.17	-0.47	0.65	0.47
19	0.74	0.54	0.17	0.75	0.49	0.13
20	0.83	0.54	0.12	-1.01	0.81	0.21
21	0.32	0.60	0.59	0.69	0.51	0.17
22	0.37	0.59	0.54	-0.80	0.75	0.29
23	-0.23	0.71	0.74	0.80	0.49	0.10
Age in years	0.40	0.06	<0.001	0.52	0.06	<0.001
Age square	-0.003	0.0004	<0.001	-0.004	0.0004	<0.001
Male (Ref=Female)	0.05	0.03	0.10	0.07	0.03	0.03
Race (Ref=Other)						
White	0.24	0.08	0.003	0.0004	0.08	1.00
Black	0.14	0.09	0.13	-0.02	0.09	0.84
Asian	-0.01	0.11	0.92	-0.33	0.11	0.002
Medicare reason for entitlement, Age (Ref=disability/ESRD)	0.21	0.05	<0.001	0.17	0.05	<0.001
Medicaid dual eligibility, No (Ref=Yes)	0.16	0.05	0.001	0.08	0.05	0.08
Marital status (Ref=Other)						

Married	0.16	0.07	0.02	0.21	0.07	0.003
Widowed	-0.11	0.07	0.14	-0.02	0.08	0.78
Divorced	-0.11	0.08	0.16	-0.03	0.08	0.68
Single	-0.14	0.08	0.10	-0.12	0.08	0.16
Area-level poverty status (Ref=Unknown)						
0% to <5%	0.04	0.12	0.73	0.13	0.12	0.25
5% to <10%	0.01	0.11	0.95	0.02	0.11	0.84
10% to <20%	-0.09	0.11	0.45	-0.04	0.11	0.69
20% to 100%	-0.17	0.11	0.12	-0.12	0.11	0.28
Urban/rural (Ref=Unknown)						
Big metro	-2.10	0.69	0.002	0.81	0.75	0.28
Metro	-2.11	0.69	0.002	0.90	0.75	0.23
Urban	-2.06	0.70	0.003	0.89	0.75	0.23
Less urban	-2.03	0.70	0.004	0.90	0.75	0.23
Rural	-2.09	0.70	0.003	1.06	0.76	0.16
SEER Registry (Ref=Greater Georgia)						
San Francisco	0.03	0.10	0.73	-0.14	0.10	0.15
Connecticut	0.03	0.08	0.70	-0.01	0.08	0.94
Detroit	-0.06	0.08	0.42	-0.03	0.08	0.72
Hawaii	-0.04	0.15	0.80	-0.31	0.16	0.05
Iowa	-0.07	0.08	0.34	0.01	0.08	0.87
New Mexico	-0.11	0.12	0.35	-0.30	0.12	0.02
Seattle	-0.27	0.08	0.001	-0.30	0.08	<0.001
Utah	-0.44	0.15	0.003	-0.22	0.14	0.11
Atlanta	-0.10	0.11	0.37	-0.08	0.11	0.49
San Jose	-0.19	0.11	0.09	-0.01	0.11	0.95
Los Angeles	-0.01	0.08	0.87	0.11	0.08	0.19
Rural Georgia	-0.55	0.36	0.13	0.20	0.32	0.53
Greater California	-0.08	0.06	0.15	-0.14	0.06	0.02
Kentucky	-0.19	0.07	0.01	-0.23	0.07	0.002
Louisiana	-0.11	0.07	0.14	-0.23	0.07	0.002
New Jersey	0.10	0.07	0.11	0.12	0.07	0.07
Stage at diagnosis (Ref=IV)						
IIIB	0.15	0.04	<0.001	0.26	0.04	<0.001
IIIC	-0.05	0.04	0.20	-0.01	0.04	0.76
Histology (Ref=NSCLC NOS)						
Non-squamous	0.05	0.05	0.32	0.06	0.05	0.21
Squamous	0.13	0.05	0.02	0.16	0.05	0.002
Brain metastasis (Ref=Unknown)						
No	0.13	0.11	0.24	0.30	0.11	0.005
Yes	-0.25	0.12	0.03	-0.01	0.11	0.95
Myocardial infarction, No (Ref=Yes)	-0.08	0.08	0.33	0.04	0.08	0.66
Congestive heart failure, No (Ref=Yes)	0.22	0.06	<0.001	0.20	0.06	0.001
Peripheral vascular disease, No (Ref=Yes)	0.01	0.05	0.88	-0.07	0.05	0.12
Cerebrovascular disease, No (Ref=Yes)	0.10	0.06	0.09	0.03	0.06	0.57
Dementia, No (Ref=Yes)	0.83	0.20	<.0001	0.67	0.19	<0.001
Chronic pulmonary disease, No (Ref=Yes)	0.04	0.03	0.22	0.12	0.03	0.001

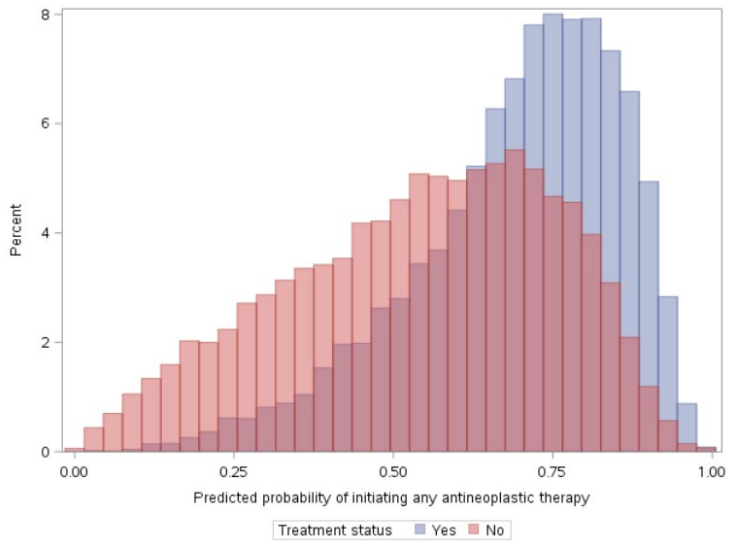
Connective tissue disease-rheumatic disease, No (Ref=Yes)	-0.01	0.08	0.89	-0.17	0.08	0.03
Peptic ulcer disease, No (Ref=Yes)	-0.08	0.15	0.60	0.21	0.15	0.17
Mild liver disease, No (Ref=Yes)	-0.17	0.10	0.09	0.06	0.10	0.56
Diabetes without complications, No (Ref=Yes)	-0.05	0.04	0.19	-0.09	0.04	0.02
Diabetes with complications, No (Ref=Yes)	0.10	0.07	0.15	0.18	0.07	0.01
Paraplegia and hemiplegia, No (Ref=Yes)	0.39	0.24	0.10	-0.17	0.24	0.48
Renal disease, No (Ref=Yes)	0.09	0.06	0.13	0.14	0.06	0.01
Moderate or severe liver disease, No (Ref=Yes)	-0.13	0.35	0.72	0.37	0.45	0.41
AIDS/HIV, No (Ref=Yes)	0.22	0.45	0.62	0.34	0.45	0.44
Proxy of poor performance status, No (Ref=Yes)	0.29	0.07	<0.001	0.54	0.07	<0.001
Home health service use, No (Ref=Yes)	0.25	0.07	<0.001	0.26	0.07	<0.001
Skilled nursing facility admission, No (Ref=Yes)	0.08	0.11	0.49	0.02	0.11	0.83
Number of inpatient admissions (Ref=≥2)						
0	0.01	0.09	0.91	-0.11	0.08	0.20
1	0.07	0.08	0.39	-0.04	0.08	0.66
Number of ER visits (Ref=≥2)						
0	0.03	0.06	0.65	0.09	0.06	0.11
1	-0.08	0.06	0.15	0.00	0.06	0.95
Annual wellness visit, No (Ref= Yes)	-0.20	0.04	<0.001	-0.18	0.04	<0.001
Flu vaccination, No (Ref= Yes)	-0.23	0.03	<0.001	-0.31	0.03	<0.001
Year of diagnosis (Ref=2015)						
2012	0.04	0.04	0.38	0.05	0.04	0.22
2013	0.01	0.04	0.72	0.03	0.04	0.47
2014	0.05	0.04	0.19	-0.02	0.04	0.58
Care at NCI cancer center No (Ref=Yes)	0.15	0.10	0.15	-0.20	0.09	0.03

Abbreviations: AIDS, acquired immunodeficiency syndrome; ER, emergency room; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; NCI, National Cancer Institute; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; Ref, reference group; SEER, Surveillance, Epidemiology, and End Results Program.

We estimated the probability of any antineoplastic therapy receipt using baseline characteristics of each patient and the model coefficients from the other random-split group. Figure 1 describes the distribution of the predicted probabilities by their actual treatment status (i.e., presence of any antineoplastic therapy claims after diagnosis). Those who had any antineoplastic therapy claims had higher predicted probability of any antineoplastic therapy receipt.

We classified patients into quintiles based on these probabilities. Table 2 describes the distribution of actual treatment status by quintile groups. Patients in the higher quintile groups were more likely to receive any antineoplastic therapy than those in the lower quintiles.

[Appendix Method 2 – Figure 1] Predicted probability of any antineoplastic therapy receipt by actual treatment status



[Appendix Method 2 – Table 2] Actual treatment status by quintile groups

n (%)	Q5 (Highest)	Q4	Q3	Q2	Q1 (Lowest)	Total
Any antineoplastic therapy[a]						
No	1512 (29.3)	2124 (41.1)	2646 (51.2)	3329 (64.4)	4163 (80.6)	13774
Yes	3656 (70.7)	3044 (58.9)	2523 (48.8)	1839 (35.6)	1005 (19.5)	12067
Total	5168	5168	5169	5168	5168	25841

[a] Presence of any antineoplastic therapy claims during the two years following diagnosis

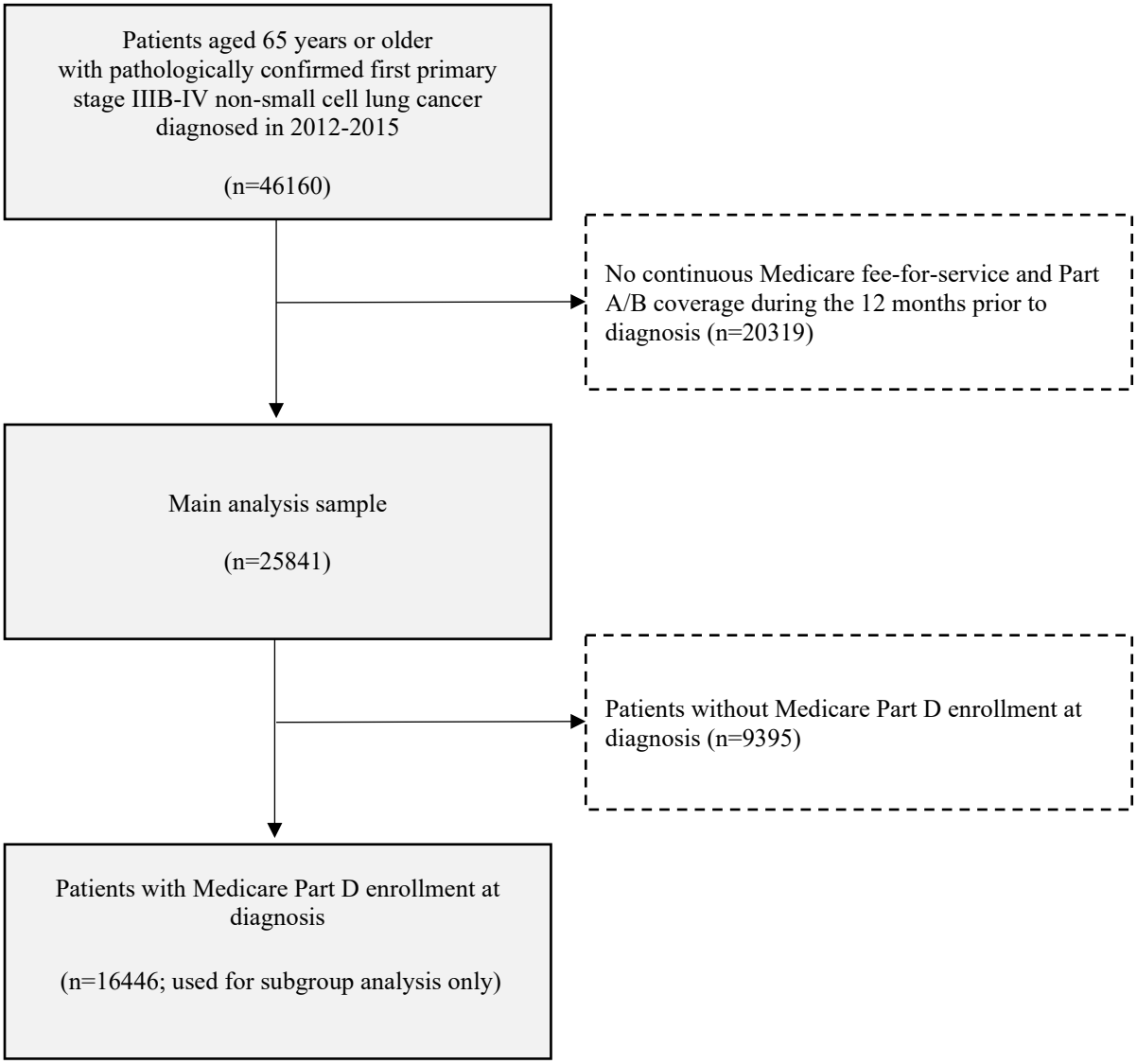
Table 3 describes the distribution of immune checkpoint inhibitor receipt by quintile groups. Among those diagnosed in 2015, patients in the higher quintile groups were also more likely to receive immune checkpoint inhibitors during the two years following diagnosis than those in the lower quintiles.

[Appendix Method 2 – Table 3] Receipt of immune checkpoint inhibitors by quintile groups among patients diagnosed in 2015

n (%)	Q5 (Highest)	Q4	Q3	Q2	Q1 (Lowest)	Total
Immune checkpoint inhibitors[a]						
No	900 (78.5)	987 (80.8)	1142 (86.7)	1147 (90.8)	1219 (94.7)	5395
Yes	244 (21.5)	234 (19.2)	175 (13.3)	116 (9.2)	68 (5.3)	839
Total	1146	1221	1317	1263	1287	6234

[a] Presence of any immune checkpoint inhibitor claims during the two years following diagnosis

[Appendix Figure 1] Cohort selection diagram



[Appendix Table 2] Baseline patient characteristics by year of diagnosis (variables not included in the main text Table 1)

	Year of diagnosis (%)			
	2012 (n=6725)	**2013** (n=6435)	**2014** (n=6447)	**2015** (n=6234)
SEER registry				
Greater California	16.8	17.6	17.5	18.0
New Jersey	13.2	14.3	14.0	14.7
Kentucky	10.0	9.2	9.3	9.6
Greater Georgia	9.6	9.5	9.9	10.2
Detroit	7.3	7.1	6.8	6.7
Louisiana	6.7	7.2	6.8	6.7
Iowa	6.0	6.0	5.7	6.2
Los Angeles	6.0	5.8	5.9	4.9
Connecticut	6.0	5.4	5.8	5.3
Seattle	5.8	5.1	6.0	5.5
San Francisco	3.3	3.7	3.4	3.3
Atlanta	2.9	2.5	2.3	2.3
San Jose	2.2	2.3	2.5	2.4
New Mexico	1.8	1.9	1.8	1.6
Utah	1.3	1.2	1.2	1.2
Hawaii	1.0	1.1	0.9	1.3
Rural Georgia	0.2	0.2	0.2	0.3
Urban/Rural				
Big metro	51.8	51.8	51.8	50.6
Metro	30.0	30.5	30.1	31.0
Urban	5.8	6.5	6.8	6.2
Less urban	9.7	8.9	9.1	9.6
Rural	NR	NR	NR	NR
Unknown	NR	NR	NR	NR
Marital status				
Married	49.7	49.7	49.4	49.9
Widowed	25.2	24.9	24.2	24.2
Divorced	10.3	11.1	10.9	11.2
Single	9.5	9.6	10.5	9.9
Other	5.4	4.8	5.1	4.9
Area-level poverty status				
0% to <5%	16.6	NR	NR	17.1
5% to <10%	24.3	24.1	24.7	26.8
10% to <20%	28.0	32.2	31.0	32.1
20% to 100%	21.2	25.8	25.0	23.9
Unknown	9.9	NR	NR	0.2
Home health service use[a]				
Yes	10.8	11.1	10.0	11.1
Skilled nursing facility admission[a]				
Yes	4.6	4.3	4.7	5.4
Number of inpatient admissions[a]				
0	74.9	77.4	77.5	75.9
1	16.9	14.7	14.7	16.0
≥2	8.2	7.9	7.8	8.1
Number of ER visits[a]				
0	63.2	63.4	62.8	61.2
1	21.3	21.7	21.1	22.1
≥2	15.4	14.9	16.2	16.6

Annual wellness visit[a,b]				
Yes	8.6	10.9	13.9	16.9
Flu vaccination[a]				
Yes	49.3	52.5	52.0	50.8
Care at NCI cancer center[c]				
Yes	2.0	1.9	2.5	2.3

Abbreviations: ER, emergency room; NCI, National Cancer Institute; NR, not reported; SEER, Surveillance, Epidemiology, and End Results Program.

[Note] Cell sizes of less than 11 were suppressed per National Cancer Institute rules to preserve patient confidentiality. If a cell size of less than 11 can be extrapolated mathematically, we also suppressed the second smallest cell.

[a] In the year prior to diagnosis.

[b] The presence of an annual appointment with the primary care provider for preventive services. Introduced to Medicare fee-for-service beneficiaries in 2011.

[c] Defined as having any claim originating at a NCI-designated cancer center in the month prior to diagnosis.

[Appendix Table 3] Cumulative percentage of treatment receipt by year of diagnosis

	2012	2013	2014	2015	Difference 2015-2012 (95% confidence interval)
Any antineoplastic therapy[a]					
One-year	45.9	45.7	46.7	45.8	-0.1 (-1.8, 1.6)
Two-year	46.7	46.7	47.9	46.7	0.0 (-1.9, 1.7)
Immune checkpoint inhibitor					
One-year	0.0	0.0	1.9	10.1	10.1 (9.4, 11.0)
Two-year	0.0	0.8	7.0	15.2	15.2 (14.1, 16.4)
Intravenous targeted therapy					
One-year	6.9	7.3	6.9	6.7	-0.2 (-1.1, 0.7)
Two-year	7.6	7.9	7.8	7.5	-0.1 (-1.1, 0.8)
Oral targeted therapy[b]					
One-year	8.4	9.8	8.4	7.4	-1.0 (-2.1, 0.2)
Two-year	9.8	11.3	9.5	8.4	-1.4 (-2.6, -0.1)

[a] Includes systemic chemotherapy, immune checkpoint inhibitors, and intravenous targeted therapy that are covered by Medicare Part A and B.

[b] Among 16446 patients with Part D enrollment at diagnosis. n=3860, 4191, 4206, and 4189 in 2012, 2013, 2014, and 2015, respectively.

[Appendix Table 4] Overall survival by year of diagnosis

	2012	2013	2014	2015	Difference 2015-2012 (95% confidence interval)
All patients					
1 year (%)	32.0	33.5	35.3	35.9	3.9 (2.3, 5.5)
2 year (%)	17.8	17.9	20.4	21.1	3.3 (2.0, 4.5)
25% survival, months	2.4	2.5	2.6	2.5	0.1 (-0.1, 0.2)
median survival, months	6.3	6.5	6.8	6.7	0.4 (0.0, 0.9)
75% survival, months	16.3	17.3	19.0	19.4	3.1 (1.9, 4.2)
Restricted mean survival at two years, months	9.3	9.4	9.8	9.9	0.6 (0.4, 0.9)
By quintiles of the predicted probability of treatment					
Q5 (Highest)					
1 year (%)	45.3	48.1	49.9	52.3	7.0 (2.9, 11.7)
2 year (%)	27.9	28.9	32.5	34.1	6.2 (2.1, 10.2)
25% survival, months	4.3	4.4	4.3	4.9	0.6 (-0.1, 1.7)
median survival, months	10.5	11.0	12.0	12.8	2.3 (1.1, 4.5)
75% survival, months	27.5	29.1	34.8	NE[a]	Not estimable
Restricted mean survival at two years, months	12.2	12.5	12.9	13.4	1.2 (0.6, 2.1)
Q4					
1 year (%)	37.2	38.4	40.5	42.3	5.1 (0.8, 9.1)
2 year (%)	21.4	20.8	23.7	26.5	5.1 (1.4, 8.6)
25% survival, months	2.9	2.9	3.5	3.1	0.2 (-0.2, 0.7)
median survival, months	7.8	8.1	8.6	9.2	1.4 (-0.1, 2.6)
75% survival, months	19.9	19.5	22.7	26.5	6.6 (1.6, 10.5)
Restricted mean survival at two years, months	10.3	10.5	11.1	11.5	1.2 (0.3, 1.8)
Q3					
1 year (%)	31.9	32.2	35.9	36.8	4.9 (-0.1, 7.9)
2 year (%)	16.7	16.7	19.8	20.9	4.2 (0.2, 6.5)
25% survival, months	2.6	2.6	2.7	2.5	-0.1 (-0.5, 0.1)
median survival, months	6.5	6.3	7.3	6.6	0.1 (-1.1, 1.1)
75% survival, months	15.8	16.2	19.1	19.8	4.0 (0.0, 6.4)
Restricted mean survival at two years, months	9.3	9.3	10.0	10.0	0.7 (-0.2, 1.2)
Q2					
1 year (%)	25.9	27.5	30.0	30.2	4.3 (1.0, 8.4)
2 year (%)	14.6	14.5	14.8	15.4	0.8 (-1.5, 4.5)
25% survival, months	2.1	2.1	2.3	2.2	0.1 (-0.3, 0.3)
median survival, months	4.9	4.8	5.3	5.3	0.4 (-0.2, 1.2)
75% survival, months	12.5	13.9	15.3	14.5	2.0 (0.3, 4.6)
Restricted mean survival at two years, months	8.0	8.2	8.6	8.5	0.5 (-0.2, 1.3)
Q1 (Lowest)					
1 year (%)	18.2	21.0	19.8	20.0	1.8 (-2.0, 4.5)
2 year (%)	7.3	8.0	10.5	9.9	2.6 (-0.1, 4.4)
25% survival, months	1.6	1.7	1.6	1.7	0.1 (-0.1, 0.3)
median survival, months	3.6	3.8	3.5	3.8	0.2 (-0.3, 0.6)
75% survival, months	8.8	10.4	9.2	9.7	0.9 (-0.7, 2.3)

Restricted mean survival at two years, months	6.2	6.7	6.5	6.6	0.4 (-0.3, 0.8)

Abbreviations: NE, not estimable.

[a] 75% survival was not reached at the end of the study for this group.

[Appendix Table 5] Cumulative mean one-year spending per patient by year of diagnosis

	2012	2013	2014	2015	Difference 2015-2012 (95% confidence interval)
All patients					
Total	55622	56131	55918	57730	2108 (616, 3668)
Acute inpatient	21824	21546	20827	20565	-1259 (-2182, -452)
Outpatient	25580	26173	27116	29352	3772 (2696, 4833)
Part D drug[a]	5254	6131	6448	6586	1332 (637, 2040)
By quintiles of the predicted probability of treatment					
Q5 (Highest)					
Total	67100	67767	64381	69121	2021 (-419, 7477)
Acute inpatient	23621	22869	21350	21048	-2573 (-4628, -58)
Outpatient	37711	38721	37230	42966	5255 (3456, 9261)
Part D drug[a]	4987	7242	7835	7388	2401 (1100, 4475)
Q4					
Total	59347	59749	60970	63567	4220 (-1426, 6132)
Acute inpatient	22959	22014	21938	21291	-1668 (-3938, 361)
Outpatient	29600	31311	32426	35614	6014 (2237, 7498)
Part D drug[a]	5612	5439	6478	8392	2780 (399, 4518)
Q3					
Total	56040	57668	58730	56509	469 (-2829, 4657)
Acute inpatient	21724	22536	21812	20242	-1482 (-3427, 877)
Outpatient	25818	26737	29218	29295	3477 (766, 5547)
Part D drug[a]	5207	6591	5790	6652	1445 (-313, 3370)
Q2					
Total	50831	50882	50778	54978	4147 (141, 7475)
Acute inpatient	21682	21672	20255	21379	-303 (-2370, 1667)
Outpatient	19772	19879	21925	24656	4884 (2264, 6365)
Part D drug[a]	5819	5983	7678	5421	-398 (-1723, 1309)
Q1 (Lowest)					
Total	43768	44486	44674	46004	2236 (-786, 5618)
Acute inpatient	18950	18563	18801	18977	27 (-2014, 1726)
Outpatient	13885	14160	14699	15961	2076 (964, 3949)
Part D drug[a]	4710	5421	4456	5352	642 (-917, 1770)

[Note] Total spending includes Medicare reimbursements for inpatient, outpatient, physician, hospice, home health care, and durable medical equipment services (Part A and B), and excludes reimbursements for oral prescriptions (Part D). Outpatient spending includes reimbursements for outpatient and physician services. Part D drug spending includes gross drug cost (i.e., price paid for the drug at the point-of-sale). All spending is reported in 2016 dollars.

[a] Examined among the subgroup of patients with part D enrollment (n=16446, 3239, 3090, 3193, 3427, and 3497 in the total sample and Q5-Q1, respectively).

[Appendix Table 6] Cumulative mean two-year spending per patient by year of diagnosis

	2012	2013	2014	2015	Difference 2015-2012 (95% confidence interval)
All patients					
Total	66848	67471	69888	72583	5735 (3479, 8040)
Acute inpatient	24895	24649	24269	23546	-1349 (-2270, -436)
Outpatient	31502	32086	35429	39163	7661 (5902, 9311)
Part D drug[a]	8119	9648	10297	11492	3373 (1890, 4769)
By quintiles of the predicted probability of treatment					
Q5 (Highest)					
Total	84213	84828	85279	93470	9257 (5120, 18617)
Acute inpatient	27935	27176	25981	26225	-1710 (-4092, 1346)
Outpatient	48294	49159	51454	59731	11437 (7964, 18066)
Part D drug[a]	8108	12176	13810	13447	5339 (2470, 8980)
Q4					
Total	72402	71853	77188	82413	10011 (1775, 14134)
Acute inpatient	26266	25164	25762	24267	-1999 (-4621, 390)
Outpatient	37090	38023	42688	49526	12436 (6627, 15427)
Part D drug[a]	9026	8684	10943	16276	7250 (2380, 10918)
Q3					
Total	66492	68426	73280	70949	4457 (-710, 8724)
Acute inpatient	25098	25470	25575	22982	-2116 (-4275, 292)
Outpatient	30841	32437	37756	38761	7920 (3580, 10745)
Part D drug[a]	7925	10350	8885	11800	3875 (380, 8437)
Q2					
Total	60109	60930	62111	66618	6509 (1764, 11020)
Acute inpatient	24151	24730	23511	24012	-139 (-2723, 2065)
Outpatient	23943	24348	27575	31405	7462 (3738, 10029)
Part D drug[a]	9167	9134	11344	9320	153 (-2584, 3982)
Q1 (Lowest)					
Total	49512	51141	51423	52204	2692 (-1297, 7157)
Acute inpatient	20762	20608	20543	20577	-185 (-2431, 1731)
Outpatient	15806	16351	17490	19092	3286 (1525, 5940)
Part D drug[a]	6583	7987	6557	7397	814 (-1457, 3153)

[Note] Total spending includes Medicare reimbursements for inpatient, outpatient, physician, hospice, home health care, and durable medical equipment services (Part A and B), and excludes reimbursements for oral prescriptions (Part D). Outpatient spending includes reimbursements for outpatient and physician services. Part D drug spending includes gross drug cost (i.e., price paid for the drug at the point-of-sale). All spending is reported in 2016 dollars.

[a] Examined among the subgroup of patients with part D enrollment (n=16446, 3239, 3090, 3193, 3427, and 3497 in the total sample and Q5-Q1, respectively).

[Appendix Table 7] Changes in survival and mean spending per patients among those with any antineoplastic therapy claim

	2012 (n=3126)	**2013** (n=2989)	**2014** (n=3069)	**2015** (n=2883)	**Difference 2015-2012 (95% confidence interval)**
Survival					
One-year survival probability, %	49.6	51.7	53.2	54.9	5.3 (2.8, 7.7)
Two-year survival probability, %	27.2	27.3	30.1	31.6	4.4 (2.1, 6.7)
25% survival, months	6.2	6.6	6.5	6.8	0.6 (0.1, 1.1)
Median survival, months	11.9	12.5	13.1	13.7	1.8 (1.1, 2.8)
75% survival, months	25.9	26.0	29.9	31.3	5.4 (2.8, 8.8)
Restricted mean survival at two years, months	13.2	13.5	13.8	14.1	0.9 (0.5, 1.3)
One-year cumulative mean spending, $					
Total	73963	75019	74484	78974	5011 (2903, 7275)
Acute inpatient	23077	22593	21724	20990	-2087 (-3331, -794)
Outpatient	43646	44915	45647	51226	7580 (5737, 9250)
Part-D drug[a]	6897	7854	7295	7571	674 (-317, 1785)
Two-year cumulative mean spending, $					
Total	93635	94982	99169	106562	12927 (9618, 16218)
Acute inpatient	28137	27789	27355	26207	-1930 (-3279, -459)
Outpatient	55148	56338	61581	70543	15395 (12543, 18076)
Part-D drug[a]	11148	12844	11941	13440	2292 (267, 4597)

[a] Examined among the subgroup of 7846 patients with part D enrollment.

[Appendix Table 8] Cumulative percentage of immune checkpoint inhibitor receipt using specific HCPCS codes only

	2012 (n=6725)	2013 (n=6435)	2014 (n=6447)	2015 (n=6234)	Difference 2015-2012 (95% confidence interval)
Immune checkpoint inhibitor					
One-year	0.0	0.0	1.0	9.2	9.2 (8.5, 10.1)
Two-year	0.0	0.4	5.5	14.4	14.4 (13.3, 15.5)

Abbreviations: HCPCS, healthcare common procedure coding system.

[Note] Excluded non-specific HCPCS codes (C9399, J9999) in 2015 claims when identifying immune checkpoint inhibitors.

[Appendix Table 9] Cumulative mean spending of patients who received immune checkpoint inhibitors using specific HCPCS codes only (descriptive analysis)

	One-year	Two-year
Total	95441 (92404, 98255)	163578 (158395, 168760)
Acute inpatient	17696 (16228, 19080)	27508 (25501, 29392)
Outpatient	72541 (70230, 74776)	125466 (120915, 129452)
Part D drug[a]	8452 (7135, 9711)	15553 (13126, 18252)

Abbreviations: HCPCS, healthcare common procedure coding system.

[Note] Results from 1158 patients with at least one immune checkpoint inhibitor claim within two years of diagnosis. Excluded non-specific HCPCS codes (C9399, J9999) in 2015 claims when identifying immune checkpoint inhibitors. Total spending includes Medicare reimbursements for inpatient, outpatient, physician, hospice, home health care, and durable medical equipment services (Part A and B), and excludes reimbursements for oral prescriptions (Part D). Outpatient spending includes reimbursements for outpatient and physician services. Part D drug spending includes gross drug cost (i.e., price paid for the drug at the point-of-sale). All spending is reported in 2016 dollars.

[a] Examined among the subgroup of patients with part D enrollment (n=793).

[Appendix Table 10] Cumulative mean spending of patients who received immune checkpoint inhibitors (descriptive analysis)

	One-year spending (95% CI)	Two-year spending (95% CI)
Total	94850 (91856, 97287)	159725 (154945, 164318)
Acute inpatient	18222 (16775, 19450)	27996 (25970, 29655)
Outpatient	71245 (69220, 73250)	121061 (116982, 124661)
Part D drug[a]	8538 (7397, 9733)	15437 (13187, 18049)

Abbreviations: CI, confidence interval.

[Note] Results from 1324 patients with at least one immune checkpoint inhibitor claim within two years of diagnosis. Total spending includes Medicare reimbursements for inpatient, outpatient, physician, hospice, home health care, and durable medical equipment services (Part A and B), and excludes reimbursements for oral prescriptions (Part D). Outpatient spending includes reimbursements for outpatient and physician services. Part D drug spending includes gross drug cost (i.e., price paid for the drug at the point-of-sale). All spending is reported in 2016 dollars.

[a] Examined among the subgroup of patients with part D enrollment (n=898).

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Chapter 2 Appendix

eTable 1. Code definitions for immune checkpoint inhibitors and other study variables

Variables	Codes
Immune checkpoint inhibitors	
Nivolumab	HCPCS: C9453, J9299 NDC: 00003377412, 00003377211, 00003373413 combined with HCPCS C9399, J3490, J3590, J9999, 96413
Pembrolizumab	HCPCS: C9027, J9271 NDC: 00006302602, 00006302902 combined with HCPCS C9399
Number of comorbid conditions[a]	
Charlson comorbidities	ICD-9-CM codes and ICD-10-CM codes for Deyo-adapted Charlson comorbidities developed by Quan et al.[1,2] Excluded codes for any malignancy and metastatic solid tumor.
Prior autoimmune conditions[b]	
Ankylosing spondylitis	ICD-9-CM: 7200 ICD-10-CM: M081, M45
Dematomyositis/polymyositis	ICD-9-CM: 7103, 7104 ICD-10-CM: M33
Felty's syndrome	ICD-9-CM: 7141 ICD-10-CM: M050
Systemic lupus erythematosus	ICD-9-CM: 7100 ICD-10-CM: M32
Polymyalgia rheumatica	ICD-9-CM: 725 ICD-10-CM: M353
Reiter's disease	ICD-9-CM: 0993 ICD-10-CM: M023
Rheumatic fever	ICD-9-CM: 390, 391, 392 ICD-10-CM: I00, I01, I02
Rheumatoid arthritis	ICD-9-CM: 714 ICD-10-CM: M05, M06, M080, M082, M083, M084, M088, M089, M120
Sarcoidosis	ICD-9-CM: 135 ICD-10-CM: D86
Sjogren's syndrome	ICD-9-CM: 7102 ICD-10-CM: M350
Systemic sclerosis/scleroderma	ICD-9-CM: 7101 ICD-10-CM: M34
Chronic rheumatic heart disease	ICD-9-CM: 393, 394, 395, 396, 397, 398 ICD-10-CM: I05, I06, I07, I08, I09
Giant cell arteritis	ICD-9-CM: 4465 ICD-10-CM: M315, M316
Polyarteritis nodosa	ICD-9-CM: 4460 ICD-10-CM: M300, M302, M308, M317
Addison's disease	ICD-9-CM: 2554 ICD-10-CM: E271, E272, E274
Chronic thyroiditis/Hashimoto thyroiditis	ICD-9-CM: 2452 ICD-10-CM: E063
Grave's disease	ICD-9-CM: 2420 ICD-10-CM: E0500, E0501
Primary biliary cirrhosis	ICD-9-CM: 5716 ICD-10-CM: K743, K745
Alopecia areata	ICD-9-CM: 70401 ICD-10-CM: L63
Dermatitis herpetiformis	ICD-9-CM: 6940 ICD-10-CM: L130

Discoid lupus erythematosus	ICD-9-CM: 6954 ICD-10-CM: L930,L932
Localized scleroderma	ICD-9-CM: 7010 ICD-10-CM: L940
Psoriasis	ICD-9-CM: 6960, 6961 ICD-10-CM: L40
Celiac disease	ICD-9-CM: 5790 ICD-10-CM: K900
Crohn's disease	ICD-9-CM: 555 ICD-10-CM: K50
Pernicious anemia	ICD-9-CM: 2810 ICD-10-CM: D510
Ulcerative colitis	ICD-9-CM: 556 ICD-10-CM: K51
Amyotrophic sclerosis	ICD-9-CM: 33520 ICD-10-CM: G1221
Multiple sclerosis	ICD-9-CM: 340 ICD-10-CM: G35
Myasthenia gravis	ICD-9-CM: 3580 ICD-10-CM: G7000, G7001
Autoimmune disease, NOS	ICD-9-CM: 27949 ICD-10-CM: D8989
Central nervous system metastasis[c]	
Secondary malignant neoplasm of brain and spinal cord	ICD-9-CM: 1983 ICD-10-CM: C793, C794
Prior Systemic therapy	
Cisplatin	HCPCS: J9062, J9060, C9418
Carboplatin	HCPCS: J9045
Paclitaxel	HCPCS: J9264, J9265, J9267, C9127, C9431
Docetaxel	HCPCS: J9170, J9171
Vinorelbine	HCPCS: J9390, C9440
Gemcitabine	HCPCS: J9201
Etoposide	HCPCS: J9181, J9182, J8560, C9414, C9425 NDC: 00378326694 in durable medical equipment claims
Pemetrexed	HCPCS: J9305, C9213
Bevacizumab	HCPCS: J9035, S0116, Q2024, C9257, C9214 Excluded ophthalmic use based on the following CPT and principal diagnosis codes CPT: 67028 ICD-9-CM: 362, 361, 365, 379, 25050, 25051, 25052, 25000 ICD-10-CM: H,E11351, E11331, E11341, E11311, E10351, E11359, E10331, E10341, E11329, E10359, E10321, E10311, E11339, E1139, E11349, E11319, E10329, E1039, E13321, E13351, E10339, E13359, E10349, E13341, E13349, E11351
Ramucirumab	HCPCS: C9025,J9308
Necitumumab	HCPCS: C9475
Oral targeted therapy[d]	
Erlotinib	NDC: 54868529000, 54868544700, 54868547400, 50242006201, 50242006301, 50242006401
Afatinib	NDC: 00597013895, 00597013790, 00597013730, 00597013830, 00597014130
Gefitinib	NDC: 00310048230, 00310048293
Osimertinib	NDC: 00310134930, 00310135030

Crizotinib	NDC: 00069814020, 00069814120
Ceritinib	NDC: 00078064070
Dabrafenib	NDC: 00078068166, 00173084608, 00173084708
Trametinib	NDC: 00078066615, 00078066815, 00173084813, 00173084913
Alectinib	NDC: 50242013001, 50242013086
Recent radiation	
Radiation	CPT: 77261-77299, 77300-77399, 77401-77499, 77520-77525, 77750-77799 ICD-9-CM: V580, V661, V671 ICD-10-CM: Z510 Revenue center: 0330, 0333 ICD-9 procedure codes: 9221-9229 ICD-10 procedure codes: 1st and 3rd character: D1 1st, 3rd, 5th character: DY7, D00, D01, D02, D04, D05, D06, DYF, DYC 1st, 3rd, 6th character: OH1 1st, 2nd, 3rd character: CW7 1st, 3rd, 5th, 7th character: D03Z 1st, 2nd, 3rd, 4th, 5th character DWY5G
Injection steroids	
Bethamethasone	HCPCS: J0702, J0704
Methylprednisolone	HCPCS: J1020, J1030, J1040, J2920, J2930
Dexamethasone	HCPCS: J1094, J1100
Prednisolone	HCPCS: J1690, J2650
Hydrocortisone	HCPCS: J1700, J1710, J1720
Triamcinolone	HCPCS: J3300, J3301, J3302, J3303
Oral steroids	
Prednisone	GNN in part D claims. HCPCS: J7512
Methylprednisolone	GNN in part D claims. HCPCS: J7509
Dexamethasone	GNN in part D claims. HCPCS: J8540
Hydrocortisone	GNN in part D claims.
Prednisolone	GNN in part D claims. HCPCS: J7510
Cortisone	GNN in part D claims.
Triamcinolone	GNN in part D claims.
Betamethasone	GNN in part D claims.
Fludrocortisone	GNN in part D claims.
Budesonide	GNN in part D claims.
Other immunosuppressants	
Hydroxychloroquine	GNN in part D claims.
Leflunomide	GNN in part D claims.
Methotrexate	GNN in part D claims. HCPCS: J9250, J9260, J8610
Sulfasalazine	GNN in part D claims.
Azathioprine	GNN in part D claims. HCPCS: J7500, J7501
Cyclophosphamide	GNN in part D claims. HCPCS: J9070, J8530
Cyclosporine	GNN in part D claims. HCPCS: J7502, J7515, J7516
Gold	GNN in part D claims. HCPCS: J1600
D-penicillamine	GNN in part D claims.
Abatacept	HCPCS: J0129
Rituximab	HCPCS: J9310
Tocilizumab	HCPCS: J3262
Adalimumab	HCPCS: J0135
Etanercept	HCPCS: J1438
Infliximab	HCPCS: J1745
Golimumab	HCPCS: J1602

Certolizumab	HCPCS: J0717

Abbreviations: CM, clinical modification; CPT, current procedural terminology; GNN, generic name variable; HCPCS, healthcare common procedure coding system; ICD, international classification of diseases; NDC, national drug code; NOS, not otherwise specified.

[a] The presence of each comorbid condition was determined by respective diagnosis codes in one or more inpatient claims or two or more outpatient/physician claims at least 30 days apart. Used all diagnosis codes available during the year prior to initiation.

[b] Identified autoimmune conditions using the ICD-9-CM codes from prior literature.[3] The presence of each condition was determined by respective diagnosis codes in one or more inpatient claims or two or more outpatient/physician claims on separate dates. ICD-9 codes were converted to ICD-10 codes based on the General Equivalence Mappings file from the Centers for Medicare and Medicaid Services and manual review. Used all diagnosis codes available during the year prior to initiation.

[c] The presence of at least one claim with respective code based on prior literature.[4] ICD-9 code was converted to ICD-10 codes based on the General Equivalence Mappings file from the Centers for Medicare and Medicaid Services and manual review. Used all diagnosis codes available during the six months prior to initiation.

[d] Generic name variable (GNN) was also used.

eTable 2. Baseline characteristics of all patients treated with immune checkpoint inhibitors

	All patients treated with immune checkpoint inhibitors during the study period (n = 4324) No. (%)
Patient characteristics	
Age at initiation, years	
<65	480 (11.10)
65-74	2167 (50.12)
75-84	1414 (32.70)
≥85	263 (6.08)
Sex	
Male	2210 (51.11)
Female	2114 (48.89)
Race	
White	3490 (80.71)
Black	379 (8.77)
Asian	184 (4.26)
Other	271 (6.27)
Medicare original reason for entitlement	
Age	3392 (78.45)
Disability/ESRD	932 (21.55)
Rural	
No	4244 (98.15)
Yes	80 (1.85)
Region	
Northeast	1008 (23.31)
Midwest	416 (9.62)
South	1116 (25.81)
West	1784 (41.26)
Tumor characteristics	
Stage at diagnosis	
I	679 (15.7)
II	246 (5.69)
III	1395 (32.26)
IV	2004 (46.35)
Histology	
Non-squamous	2618 (60.55)
Squamous	1360 (31.45)
NSCLC NOS	346 (8.00)

Abbreviations: ESRD, end-stage renal disease; NOS, not otherwise specified; NSCLC, non-small cell lung cancer.

eTable 3. Multivariable survival analysis among patients with non-squamous histology

Variables	Patients with non-squamous cancer (n=793) No. (%)	Multivariable[a]		p
		HR	95% CI	
Patient characteristics				
Age at initiation, years				
65-74	373 (47.04)	ref		
75-84	348 (43.88)	1.00	(0.82, 1.21)	0.57
≥85	72 (9.08)	0.84	(0.59, 1.18)	
Sex				
Male	371 (46.78)	ref		0.21
Female	422 (53.22)	0.89	(0.74, 1.07)	
Race				
White	668 (84.24)	ref		
Black	57 (7.19)	1.38	(0.99, 1.92)	0.20
Asian	28 (3.53)	1.34	(0.81, 2.23)	
Other	40 (5.04)	1.05	(0.67, 1.65)	
Medicare original reason for entitlement				
Age	710 (89.53)	ref		0.82
Disability/ESRD	83 (10.47)	0.96	(0.71, 1.32)	
Medicaid dual eligibility[b]				
No	688 (86.76)	ref		0.14
Yes	105 (13.24)	0.80	(0.59, 1.08)	
Rural				
No	775 (97.73)	ref		0.37
Yes	18 (2.27)	0.75	(0.40, 1.41)	
Region				
Northeast	203 (25.6)	ref		
Midwest	83 (10.47)	1.34	(0.97, 1.85)	0.03
South	171 (21.56)	1.32	(1.00, 1.72)	
West	336 (42.37)	0.95	(0.75, 1.21)	
Number of comorbid conditions[c]				
0	185 (23.33)	ref		
1	240 (30.26)	1.08	(0.84, 1.40)	0.11
≥2	368 (46.41)	1.27	(1.00, 1.62)	
Proxy of performance status[c]				
ECOG 0-1	707 (89.16)	ref		0.06
ECOG 2-4	86 (10.84)	1.33	(0.99, 1.80)	
Prior autoimmune conditions[c]				
No	678 (85.50)	ref		0.04
Yes	115 (14.50)	1.29	(1.01, 1.65)	
Tumor characteristics				
Stage at diagnosis				
I	134 (16.90)	ref		
II	39 (4.92)	1.26	(0.78, 2.01)	0.42
III	243 (30.64)	1.24	(0.92, 1.67)	
IV	377 (47.54)	1.09	(0.82, 1.45)	
Central nervous system metastasis[d]				
No	647 (81.59)	ref		0.56
Yes	146 (18.41)	1.07	(0.85, 1.36)	
Treatment history				
Prior systemic therapy[e]				
Platinum doublets	336 (42.37)	ref		0.02

None	66 (8.32)	1.14	(0.78, 1.67)	
Single chemotherapy	30 (3.78)	1.70	(1.05, 2.74)	
Platinum doublets + bevacizumab	141 (17.78)	1.23	(0.95, 1.59)	
Other	220 (27.74)	1.41	(1.13, 1.77)	
Prior oral targeted therapy[f]				
No	414 (52.21)	ref		
Yes	92 (11.6)	0.96	(0.69, 1.33)	0.67
Unknown	287 (36.19)	1.08	(0.88, 1.32)	
Recent radiation[g]				
No	711 (89.66)	ref		0.05
Yes	82 (10.34)	1.33	(1.01, 1.76)	
Care at NCI-designated cancer center[h]				
No	635 (80.08)	ref		0.98
Yes	158 (19.92)	1.00	(0.79, 1.27)	
Time from diagnosis to initiation				
2 - 6 months	21 (2.65)	ref		
6 months - 1 year	189 (23.83)	0.53	(0.32, 0.88)	<0.001
1 - 3 years	417 (52.59)	0.41	(0.25, 0.67)	
>3 years	166 (20.93)	0.34	(0.19, 0.58)	

Abbreviation: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESRD, end-stage renal disease; HR, hazard ratio; NCI, National Cancer Institute; p, p-value; ref, reference group.

[a] Results from a multivariable Cox proportional hazard model with all variables listed in the table. P values were calculated from Wald tests.

[b] Any state buy-in in the year prior to initiation.

[c] In the year prior to initiation.

[d] In the 6 months prior to initiation.

[e] Since diagnosis. Includes chemotherapy and infusion targeted therapy. Excludes oral targeted therapy.

[f] Since diagnosis. Includes epidermal growth factor receptor tyrosine kinase (EGFR TKIs), anaplastic lymphoma kinase (ALK) and ROS1, BRAF and MEK inhibitors. Unknown status for those without continuous Medicare Part D coverage.

[g] In the 30 days prior to initiation.

[h] Defined as having any claim originating at a NCI-designated cancer center in the 90 days prior to initiation.

eTable 4. Multivariable survival analysis among patients with squamous histology

Variables	Patients with squamous cancer (n=372) No. (%)[a]	Multivariable[b]		p
		HR	95% CI	
Patient characteristics				
Age at initiation, years				
65-74	183 (49.19)	ref		
75-84	163 (43.82)	1.00	(0.76, 1.33)	0.88
≥85	26 (6.99)	0.87	(0.50, 1.53)	
Sex				
Male	234 (62.90)	ref		0.74
Female	138 (37.10)	0.96	(0.74, 1.24)	
Race				
White	329 (88.44)	ref		
Black	26 (6.99)	1.01	(0.62, 1.64)	0.18
Asian	NR	2.64	(1.12, 6.23)	
Other	NR	1.06	(0.47, 2.40)	
Medicare original reason for entitlement				
Age	304 (81.72)	ref		0.92
Disability/ESRD	68 (18.28)	1.02	(0.73, 1.43)	
Medicaid dual eligibility[c]				
No	302 (81.18)	ref		0.74
Yes	70 (18.82)	1.06	(0.76, 1.49)	
Rural				
No	NR	ref		0.37
Yes	NR	0.65	(0.26, 1.65)	
Region				
Northeast	76 (20.43)	ref		
Midwest	50 (13.44)	0.60	(0.38, 0.96)	0.15
South	121 (32.53)	0.95	(0.67, 1.35)	
West	125 (33.60)	0.90	(0.63, 1.29)	
Number of comorbid conditions[d]				
0	48 (12.90)	ref		
1	117 (31.45)	1.57	(0.99, 2.48)	0.003
≥2	207 (55.65)	2.03	(1.32, 3.13)	
Proxy of performance status[d]				
ECOG 0-1	322 (86.56)	ref		0.59
ECOG 2-4	50 (13.44)	1.11	(0.76, 1.61)	
Prior autoimmune conditions[d]				
No	333 (89.52)	ref		0.99
Yes	39 (10.48)	1.00	(0.65, 1.52)	
Tumor characteristics				
Stage at diagnosis				
I	81 (21.77)	ref		
II	31 (8.33)	1.10	(0.67, 1.83)	0.37
III	146 (39.25)	0.98	(0.69, 1.39)	
IV	114 (30.65)	0.78	(0.53, 1.14)	
Central nervous system metastasis[e]				
No	338 (90.86)	ref		0.01
Yes	34 (9.14)	1.69	(1.11, 2.58)	
Treatment history				
Prior systemic therapy[f]				
Platinum doublets	245 (65.86)	ref		0.24

None	34 (9.14)	1.07	(0.67, 1.69)	
Single chemotherapy	NR	2.07	(1.02, 4.21)	
Platinum doublets + bevacizumab	NR	2.15	(0.49, 9.35)	
Other	80 (21.51)	1.14	(0.81, 1.60)	
Prior oral targeted therapy[g]				
No	238 (63.98)	ref		
Yes	14 (3.76)	0.89	(0.45, 1.75)	0.40
Unknown	120 (32.26)	1.19	(0.91, 1.56)	
Recent radiation[h]				
No	338 (90.86)	ref		<0.001
Yes	34 (9.14)	2.42	(1.59, 3.67)	
Care at NCI-designated cancer center[i]				
No	317 (85.22)	ref		0.49
Yes	55 (14.78)	1.14	(0.79, 1.63)	
Time from diagnosis to initiation				
2 - 6 months	18 (4.84)	ref		
6 months - 1 year	103 (27.69)	1.30	(0.67, 2.50)	0.38
1 - 3 years	195 (52.42)	1.07	(0.56, 2.04)	
>3 years	56 (15.05)	0.90	(0.43, 1.87)	

Abbreviation: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESRD, end-stage renal disease; HR, hazard ratio; NCI, National Cancer Institute; NR, not reported; p, p-value; ref, reference group.

[a] Cell sizes of less than 11 were suppressed per NCI rules to preserve patient confidentiality. If a cell size of less than 11 can be extrapolated mathematically, we also suppressed the second smallest cell.

[b] Results from a multivariable Cox proportional hazard model with all variables listed in the table. P values were calculated from Wald tests.

[c] Any state buy-in in the year prior to initiation.

[d] In the year prior to initiation.

[e] In the 6 months prior to initiation.

[f] Since diagnosis. Includes chemotherapy and infusion targeted therapy. Excludes oral targeted therapy.

[g] Since diagnosis. Includes epidermal growth factor receptor tyrosine kinase (EGFR TKIs), anaplastic lymphoma kinase (ALK) and ROS1, BRAF and MEK inhibitors. Unknown status for those without continuous Medicare Part D coverage.

[h] In the 30 days prior to initiation.

[i] Defined as having any claim originating at a NCI-designated cancer center in the 90 days prior to initiation.

eTable 5. Multivariable survival analysis among patients with stage I-III at diagnosis

Variables	Patients with stage I-III at diagnosis (n=721) No. (%)	Multivariable[a]		p
		HR	95% CI	
Patient characteristics				
Age at initiation, years				
65-74	327 (45.35)	ref		
75-84	327 (45.35)	0.87	(0.71, 1.06)	0.34
≥85	67 (9.29)	0.86	(0.60, 1.24)	
Sex				
Male	382 (52.98)	ref		0.47
Female	339 (47.02)	1.07	(0.89, 1.30)	
Race				
White	628 (87.10)	ref		
Black	39 (5.41)	1.14	(0.76, 1.71)	0.13
Asian	23 (3.19)	1.83	(1.09, 3.09)	
Other	31 (4.30)	1.15	(0.72, 1.84)	
Medicare original reason for entitlement				
Age	615 (85.30)	ref		0.40
Disability/ESRD	106 (14.70)	0.89	(0.67, 1.17)	
Medicaid dual eligibility[b]				
No	614 (85.16)	ref		0.22
Yes	107 (14.84)	0.83	(0.63, 1.11)	
Rural				
No	709 (98.34)	ref		0.43
Yes	12 (1.66)	0.72	(0.31, 1.64)	
Region				
Northeast	183 (25.38)	ref		
Midwest	80 (11.10)	0.85	(0.61, 1.21)	0.17
South	184 (25.52)	1.20	(0.93, 1.57)	
West	274 (38.00)	0.98	(0.77, 1.25)	
Number of comorbid conditions[c]				
0	129 (17.89)	ref		
1	222 (30.79)	1.27	(0.95, 1.70)	<0.001
≥2	370 (51.32)	1.71	(1.30, 2.26)	
Proxy of performance status[c]				
ECOG 0-1	641 (88.90)	ref		0.79
ECOG 2-4	80 (11.10)	1.04	(0.77, 1.42)	
Prior autoimmune conditions[c]				
No	634 (87.93)	ref		0.31
Yes	87 (12.07)	1.15	(0.88, 1.51)	
Tumor characteristics				
Histology				
Non-squamous	416 (57.70)	ref		
Squamous	258 (35.78)	1.43	(1.16, 1.76)	0.004
NSCLC NOS	47 (6.52)	1.19	(0.83, 1.70)	
Central nervous system metastasis[d]				
No	642 (89.04)	ref		0.06
Yes	79 (10.96)	1.33	(0.99, 1.79)	
Treatment history				
Prior systemic therapy[e]				
Platinum doublets	366 (50.76)	ref		0.04
None	74 (10.26)	1.08	(0.78, 1.50)	

Single chemotherapy	34 (4.72)	1.50	(0.97, 2.31)	
Platinum doublets + bevacizumab	55 (7.63)	1.62	(1.13, 2.32)	
Other	192 (26.63)	1.26	(1.00, 1.60)	
Prior oral targeted therapy[f]				
No	416 (57.70)	ref		
Yes	56 (7.77)	1.01	(0.70, 1.48)	0.14
Unknown	249 (34.54)	1.22	(1.00, 1.50)	
Recent radiation[g]				
No	647 (89.74)	ref		0.09
Yes	74 (10.26)	1.30	(0.96, 1.76)	
Care at NCI-designated cancer center[h]				
No	587 (81.41)	ref		0.29
Yes	134 (18.59)	1.14	(0.89, 1.45)	
Time from diagnosis to initiation				
2 - 6 months	15 (2.08)	ref		
6 months - 1 year	147 (20.39)	0.84	(0.46, 1.52)	0.002
1 - 3 years	392 (54.37)	0.64	(0.36, 1.14)	
>3 years	167 (23.16)	0.49	(0.26, 0.90)	

Abbreviation: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESRD, end-stage renal disease; HR, hazard ratio; NCI, National Cancer Institute; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; p, p-value; ref, reference group.

[a] Results from a multivariable Cox proportional hazard model with all variables listed in the table. P values were calculated from Wald tests.

[b] Any state buy-in in the year prior to initiation.

[c] In the year prior to initiation.

[d] In the 6 months prior to initiation.

[e] Since diagnosis. Includes chemotherapy and infusion targeted therapy. Excludes oral targeted therapy.

[f] Since diagnosis. Includes epidermal growth factor receptor tyrosine kinase (EGFR TKIs), anaplastic lymphoma kinase (ALK) and ROS1, BRAF and MEK inhibitors. Unknown status for those without continuous Medicare Part D coverage.

[g] In the 30 days prior to initiation.

[h] Defined as having any claim originating at a NCI-designated cancer center in the 90 days prior to initiation.

eTable 6. Multivariable survival analysis among patients with stage IV at diagnosis

Variables	Patients with stage IV at diagnosis (n=535) No. (%)	Multivariable[a]		p
		HR	95% CI	
Patient characteristics				
Age at initiation, years				
65-74	278 (51.96)	ref		
75-84	218 (40.75)	1.16	(0.92, 1.46)	0.31
≥85	39 (7.29)	0.88	(0.56, 1.40)	
Sex				
Male	271 (50.65)	ref		0.29
Female	264 (49.35)	0.89	(0.71, 1.11)	
Race				
White	444 (82.99)	ref		
Black	50 (9.35)	1.19	(0.83, 1.71)	0.58
Asian	14 (2.62)	0.74	(0.35, 1.55)	
Other	27 (5.05)	0.84	(0.48, 1.46)	
Medicare original reason for entitlement				
Age	479 (89.53)	ref		0.24
Disability/ESRD	56 (10.47)	1.24	(0.87, 1.78)	
Medicaid dual eligibility[b]				
No	457 (85.42)	ref		0.68
Yes	78 (14.58)	0.93	(0.67, 1.30)	
Rural				
No	519 (97.01)	ref		0.52
Yes	16 (2.99)	0.81	(0.43, 1.53)	
Region				
Northeast	124 (23.18)	ref		
Midwest	63 (11.78)	1.06	(0.72, 1.54)	0.95
South	124 (23.18)	1.10	(0.79, 1.54)	
West	224 (41.87)	1.02	(0.76, 1.36)	
Number of comorbid conditions[c]				
0	124 (23.18)	ref		
1	170 (31.78)	1.05	(0.78, 1.41)	0.82
≥2	241 (45.05)	1.10	(0.82, 1.47)	
Proxy of performance status[c]				
ECOG 0-1	471 (88.04)	ref		0.27
ECOG 2-4	64 (11.96)	1.21	(0.86, 1.70)	
Prior autoimmune conditions[c]				
No	464 (86.73)	ref		0.96
Yes	71 (13.27)	1.01	(0.73, 1.39)	
Tumor characteristics				
Histology				
Non-squamous	377 (70.47)	ref		
Squamous	114 (21.31)	1.05	(0.79, 1.38)	0.95
NSCLC NOS	44 (8.22)	1.00	(0.67, 1.50)	
Central nervous system metastasis[d]				
No	414 (77.38)	ref		0.52
Yes	121 (22.62)	1.09	(0.84, 1.43)	
Treatment history				
Prior systemic therapy[e]				
Platinum doublets	258 (48.22)	ref		0.18
None	28 (5.23)	0.99	(0.57, 1.72)	

Single chemotherapy	12 (2.24)	1.66	(0.83, 3.32)	
Platinum doublets + bevacizumab	100 (18.69)	1.11	(0.81, 1.51)	
Other	137 (25.61)	1.37	(1.04, 1.82)	
Prior oral targeted therapy[f]				
No	290 (54.21)	ref		
Yes	58 (10.84)	1.00	(0.67, 1.50)	0.63
Unknown	187 (34.95)	0.89	(0.70, 1.14)	
Recent radiation[g]				
No	477 (89.16)	ref		0.002
Yes	58 (10.84)	1.69	(1.22, 2.34)	
Care at NCI-designated cancer center[h]				
No	430 (80.37)	ref		0.44
Yes	105 (19.63)	0.89	(0.67, 1.19)	
Time from diagnosis to initiation				
2 - 6 months	31 (5.79)	ref		
6 months - 1 year	172 (32.15)	0.75	(0.48, 1.18)	0.03
1 - 3 years	266 (49.72)	0.60	(0.38, 0.95)	
>3 years	66 (12.34)	0.47	(0.26, 0.83)	

Abbreviation: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESRD, end-stage renal disease; HR, hazard ratio; NCI, National Cancer Institute; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; p, p-value; ref, reference group.

[a] Results from a multivariable Cox proportional hazard model with all variables listed in the table. P values were calculated from Wald tests.

[b] Any state buy-in in the year prior to initiation.

[c] In the year prior to initiation.

[d] In the 6 months prior to initiation.

[e] Since diagnosis. Includes chemotherapy and infusion targeted therapy. Excludes oral targeted therapy.

[f] Since diagnosis. Includes epidermal growth factor receptor tyrosine kinase (EGFR TKIs), anaplastic lymphoma kinase (ALK) and ROS1, BRAF and MEK inhibitors. Unknown status for those without continuous Medicare Part D coverage.

[g] In the 30 days prior to initiation.

[h] Defined as having any claim originating at a NCI-designated cancer center in the 90 days prior to initiation.

eTable 7. Baseline steroid or other immunosuppressant use by prior autoimmune disease status[a]

n (%)	With prior autoimmune disease	Without prior autoimmune disease
Steroids		
Injection only[b]	74 (46.8%)	351 (32.0%)
Injection and oral[c]	73 (67.6%)	380 (47.1%)
Other immunosuppressant use[c]	12 (11.1%)	Not reported[d]

[a]Baseline steroid or other immunosuppressant use during the 60 days prior to immune checkpoint inhibitor initiation. Steroids include prednisone, methylprednisolone, dexamethasone, hydrocortisone, prednisolone, cortisone, triamcinolone, betamethasone, fludrocortisone, and budesonide. Other immunosuppressants include hydroxychloroquine, leflunomide, methotrexate, sulfasalazine, azathioprine, cyclophosphamide, cyclosporine, gold, d-penicillamine, abatacept, rituximab, tocilizumab, adalimumab, etanercept, infliximab, golimumab, and certolizumab.

[b]Among all patients included in the study (n=158 and n=1,098 for those with and without prior autoimmune disease, respectively).

[c]Among subgroup of patients with Medicare Part D coverage during the 60 days prior to immune checkpoint inhibitor injection (n=108 and n=807 for those with and without prior autoimmune disease, respectively).

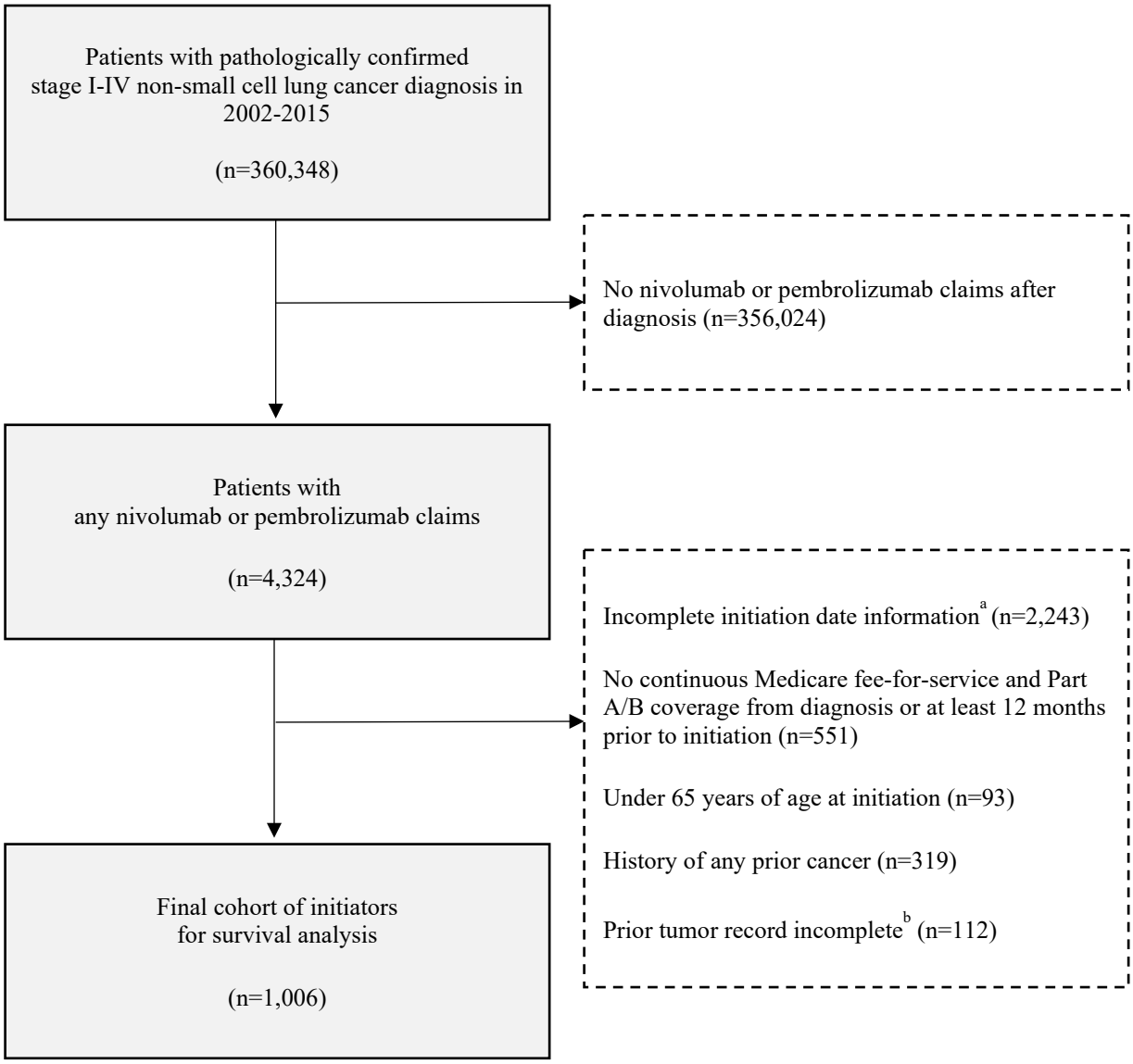
[d]Cell sizes of less than 11 were suppressed per National Cancer Institute rule to preserve patient confidentiality.

eTable 8. Median survival stratified by prior autoimmune disease and baseline injection steroid use in the main cohort[a]

		n	Median survival month (95% CI)	p
With prior autoimmune disease	Injection steroids	74	5.1 (4.4-8.5)	0.06
	No injection steroids	84	11.9 (10.0-15.6)	
Without prior autoimmune disease	Injection steroids	351	8.6 (7.4-10.7)	
	No injection steroids	747	9.7 (8.6-11.2)	

[a]Unadjusted Kaplan-Meier survival analysis. Includes all patients included in the study (n=1256). P-value is from log-rank test.

eFigure 1. Cohort selection diagram for analyses restricted to patients without history of any other cancer



[a] First immune checkpoint inhibitor claim prior to March 1, 2016 (two months after Healthcare Common Procedure Coding System J codes became available).

[b] Lung cancer was not the first primary malignant cancer, but information on prior disease was unavailable.

eTable 9. Analyses restricted to patients without history of any other cancer

Variables	Cohort (n=1006) No. (%)	Multivariable[a] HR	95% CI	p
Patient characteristics				
Age at initiation, years				
65-74	502 (49.90)	ref		
75-84	427 (42.45)	1.09	(0.92, 1.28)	0.19
≥85	77 (7.65)	0.82	(0.59, 1.14)	
Sex				
Male	505 (50.20)	ref		0.78
Female	501 (49.80)	1.02	(0.87, 1.20)	
Race				
White	860 (85.49)	ref		
Black	68 (6.76)	1.05	(0.77, 1.42)	0.83
Asian	28 (2.78)	1.24	(0.76, 2.03)	
Other	50 (4.97)	0.97	(0.66, 1.42)	
Medicare original reason for entitlement				
Age	877 (87.18)	ref		0.50
Disability/ESRD	129 (12.82)	1.09	(0.86, 1.38)	
Medicaid dual eligibility[b]				
No	846 (84.10)	ref		0.10
Yes	160 (15.90)	0.82	(0.65, 1.04)	
Rural				
No	982 (97.61)	ref		0.22
Yes	24 (2.39)	0.72	(0.42, 1.22)	
Region				
Northeast	251 (24.95)	ref		
Midwest	111 (11.03)	1.01	(0.76, 1.34)	0.12
South	257 (25.55)	1.28	(1.02, 1.61)	
West	387 (38.47)	1.05	(0.85, 1.29)	
Number of comorbid conditions[c]				
0	193 (19.18)	ref		
1	326 (32.41)	1.20	(0.95, 1.51)	<0.001
≥2	487 (48.41)	1.56	(1.25, 1.95)	
Proxy of performance status[c]				
ECOG 0-1	888 (88.27)	ref		0.36
ECOG 2-4	118 (11.73)	1.12	(0.88, 1.44)	
Prior autoimmune conditions[c]				
No	876 (87.08)	ref		0.91
Yes	130 (12.92)	1.01	(0.81, 1.27)	
Tumor Characteristics				
Stage at diagnosis				
I	169 (16.80)	ref		
II	59 (5.86)	1.06	(0.73, 1.54)	0.54
III	341 (33.90)	1.07	(0.84, 1.37)	
IV	437 (43.44)	0.94	(0.73, 1.20)	
Histology				
Non-squamous	631 (62.72)	ref		
Squamous	304 (30.22)	1.30	(1.08, 1.56)	0.02
NSCLC NOS	71 (7.06)	1.18	(0.87, 1.59)	
Central nervous system metastasis[d]				
No	837 (83.20)	ref		0.79
Yes	169 (16.80)	1.03	(0.83, 1.28)	

Treatment Characteristics				
Prior systemic therapy[e]				
Platinum doublets	499 (49.60)	ref		
None	78 (7.75)	1.11	(0.80, 1.52)	
Single chemotherapy	38 (3.78)	1.47	(0.98, 2.22)	0.001
Platinum doublets + bevacizumab	132 (13.12)	1.28	(0.99, 1.66)	
Other	259 (25.75)	1.50	(1.23, 1.84)	
Prior oral targeted therapy[f]				
No	583 (57.95)	ref		
Yes	82 (8.15)	1.02	(0.75, 1.39)	0.69
Unknown	341 (33.90)	1.08	(0.91, 1.28)	
Recent radiation[g]				
No	895 (88.97)	ref		<0.001
Yes	111 (11.03)	1.63	(1.28, 2.07)	
Care at NCI-designated cancer center[h]				
No	819 (81.41)	ref		0.79
Yes	187 (18.59)	1.03	(0.84, 1.27)	
Time from diagnosis to initiation				
2 - 6 months	33 (3.28)	ref		
6 months - 1 year	265 (26.34)	0.91	(0.60, 1.39)	0.001
1 - 3 years	536 (53.28)	0.69	(0.45, 1.05)	
>3 years	172 (17.10)	0.56	(0.35, 0.89)	

Abbreviation: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESRD, end-stage renal disease; HR, hazard ratio; NCI, National Cancer Institute; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; p, p-value; ref, reference group.

[a] Results from a multivariable Cox proportional hazard model with all variables listed in the table. P values were calculated from Wald tests.

[b] Any state buy-in in the year prior to initiation.

[c] In the year prior to initiation.

[d] In the 6 months prior to initiation.

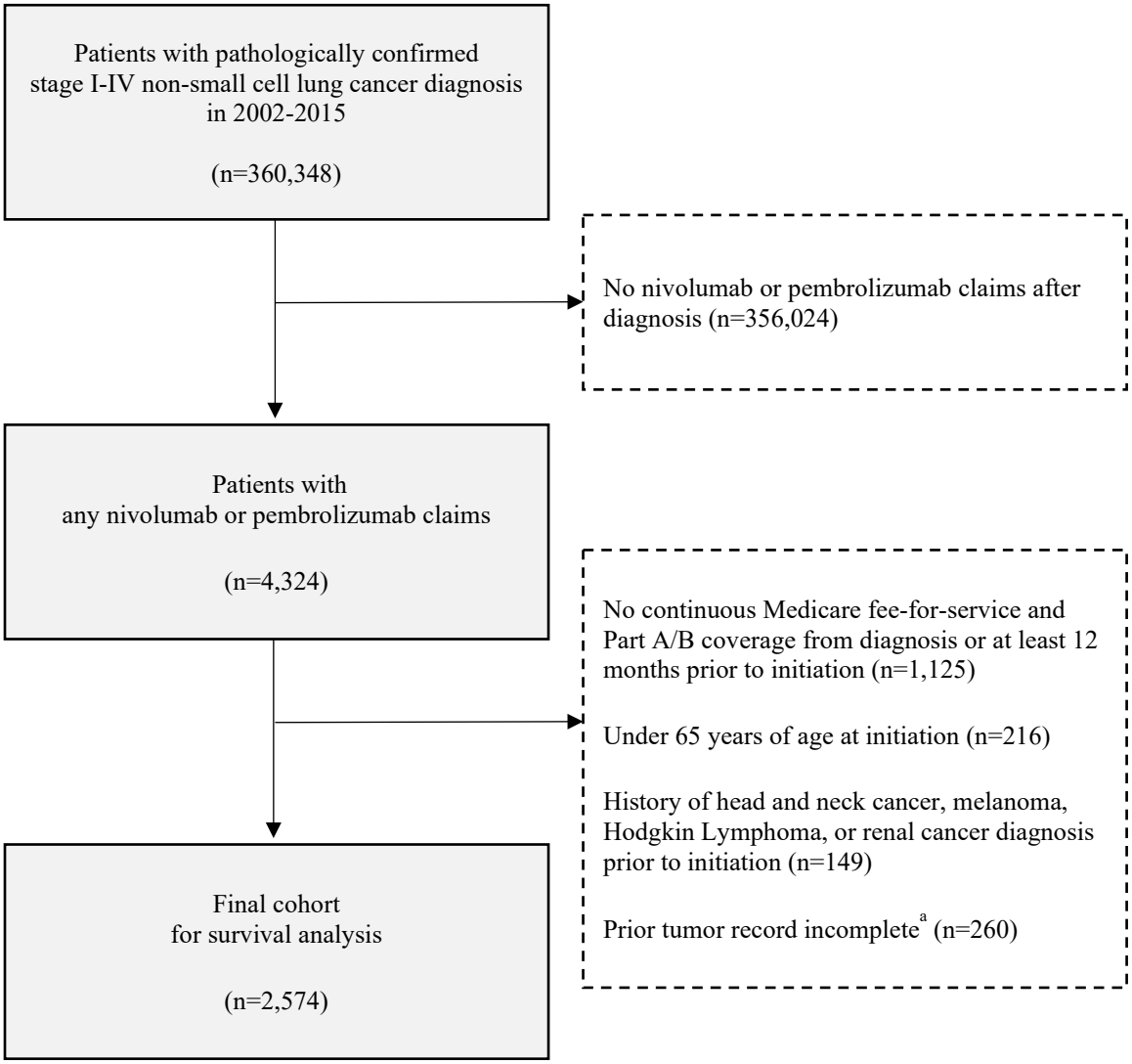
[e] Since diagnosis. Includes chemotherapy and infusion targeted therapy. Excludes oral targeted therapy.

[f] Since diagnosis. Includes epidermal growth factor receptor tyrosine kinase (EGFR TKIs), anaplastic lymphoma kinase (ALK) and ROS1, BRAF and MEK inhibitors. Unknown status for those without continuous Medicare Part D coverage.

[g] In the 30 days prior to initiation.

[h] Defined as having any claim originating at a NCI-designated cancer center in the 90 days prior to initiation.

eFigure 2. Cohort selection diagram for analyses including patients with first immune checkpoint inhibitor claim prior to March 2016



[a] Lung cancer was not the first primary malignant cancer, but information on prior disease was unavailable.

eTable 10. Analyses including patients with first immune checkpoint inhibitor claim prior to March 2016

Variables	Cohort (n=2574) No. (%)	Multivariable[a] HR	95% CI	p
Patient characteristics				
Age at initiation, years				
65-74	1299 (50.47)	ref		0.85
75-84	1072 (41.65)	0.99	(0.90, 1.09)	
≥85	203 (7.89)	0.95	(0.79, 1.14)	
Sex				
Male	1311 (50.93)	ref		0.19
Female	1263 (49.07)	0.94	(0.86, 1.03)	
Race				
White	2171 (84.34)	ref		0.12
Black	181 (7.03)	1.12	(0.94, 1.34)	
Asian	94 (3.65)	1.31	(1.01, 1.68)	
Other	128 (4.97)	1.10	(0.88, 1.36)	
Medicare original reason for entitlement				
Age	2255 (87.61)	ref		0.98
Disability/ESRD	319 (12.39)	1.00	(0.87, 1.16)	
Medicaid dual eligibility[b]				
No	2188 (85.00)	ref		0.05
Yes	386 (15.00)	0.87	(0.75, 1.00)	
Rural				
No	2524 (98.06)	ref		0.23
Yes	50 (1.94)	0.81	(0.57, 1.14)	
Region				
Northeast	623 (24.20)	ref		0.56
Midwest	266 (10.33)	1.06	(0.89, 1.25)	
South	632 (24.55)	1.08	(0.94, 1.23)	
West	1053 (40.91)	0.99	(0.88, 1.12)	
Number of comorbid conditions[c]				
0	533 (20.71)	ref		0.003
1	799 (31.04)	1.06	(0.93, 1.21)	
≥2	1242 (48.25)	1.22	(1.07, 1.38)	
Proxy of performance status[c]				
ECOG 0-1	2268 (88.11)	ref		0.001
ECOG 2-4	306 (11.89)	1.29	(1.12, 1.49)	
Prior autoimmune conditions[c]				
No	2274 (88.34)	ref		0.53
Yes	300 (11.66)	0.96	(0.83, 1.10)	
Tumor Characteristics				
Stage at diagnosis				
I	390 (15.15)	ref		0.34
II	137 (5.32)	1.13	(0.90, 1.42)	
III	828 (32.17)	1.05	(0.90, 1.22)	
IV	1219 (47.36)	0.97	(0.83, 1.12)	
Histology				
Non-squamous	1554 (60.37)	ref		0.07
Squamous	818 (31.78)	1.13	(1.01, 1.25)	
NSCLC NOS	202 (7.85)	0.98	(0.83, 1.17)	
Central nervous system metastasis[d]				
No	2148 (83.45)	ref		0.15

Yes	426 (16.55)	1.10	(0.97, 1.25)	
Treatment Characteristics				
Prior systemic therapy[e]				
Platinum doublets	1207 (46.89)	ref		
None	189 (7.34)	0.93	(0.76, 1.12)	
Single chemotherapy	93 (3.61)	1.13	(0.89, 1.44)	0.01
Platinum doublets + bevacizumab	254 (9.87)	1.13	(0.96, 1.34)	
Other	831 (32.28)	1.20	(1.07, 1.34)	
Prior oral targeted therapy[f]				
No	1470 (57.11)	ref		
Yes	240 (9.32)	1.02	(0.86, 1.21)	0.97
Unknown	864 (33.57)	1.01	(0.91, 1.12)	
Recent radiation[g]				
No	2300 (89.36)	ref		<0.001
Yes	274 (10.64)	1.51	(1.31, 1.75)	
Care at NCI-designated cancer center[h]				
No	2036 (79.10)	ref		0.84
Yes	538 (20.9)	1.01	(0.90, 1.14)	
Time from diagnosis to initiation				
2 - 6 months	215 (8.35)	ref		
6 months - 1 year	680 (26.42)	0.83	(0.70, 0.99)	<0.001
1 - 3 years	1234 (47.94)	0.63	(0.53, 0.75)	
>3 years	445 (17.29)	0.56	(0.45, 0.68)	

Abbreviation: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESRD, end-stage renal disease; HR, hazard ratio; NCI, National Cancer Institute; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; p, p-value; ref, reference group.

[a] Results from a multivariable Cox proportional hazard model with all variables listed in the table. P values were calculated from Wald tests.

[b] Any state buy-in in the year prior to initiation.

[c] In the year prior to initiation.

[d] In the 6 months prior to initiation.

[e] Since diagnosis. Includes chemotherapy and infusion targeted therapy. Excludes oral targeted therapy.

[f] Since diagnosis. Includes epidermal growth factor receptor tyrosine kinase (EGFR TKIs), anaplastic lymphoma kinase (ALK) and ROS1, BRAF and MEK inhibitors. Unknown status for those without continuous Medicare Part D coverage.

[g] In the 30 days prior to initiation.

[h] Defined as having any claim originating at a NCI-designated cancer center in the 90 days prior to initiation.

eTable 11. Multivariable survival analyses using a 1-year covariate assessment period to identify central nervous system metastasis[a]

Variables	Multivariable[b]		p
	HR	95% CI	
Patient characteristics			
Age at initiation, years			
65-74	ref		
75-84	1.00	(0.86, 1.16)	0.64
≥85	0.88	(0.67, 1.16)	
Sex			
Male	ref		0.75
Female	0.98	(0.85, 1.13)	
Race			
White	ref		
Black	1.16	(0.89, 1.51)	0.38
Asian	1.35	(0.89, 2.06)	
Other	0.99	(0.70, 1.41)	
Medicare original reason for entitlement			
Age	ref		0.91
Disability/ESRD	1.01	(0.82, 1.26)	
Medicaid dual eligibility[c]			
No	ref		0.15
Yes	0.85	(0.69, 1.06)	
Rural			
No	ref		0.28
Yes	0.76	(0.46, 1.25)	
Region			
Northeast	ref		
Midwest	0.95	(0.74, 1.22)	0.14
South	1.19	(0.97, 1.46)	
West	0.98	(0.82, 1.17)	
Number of comorbid conditions[d]			
0	ref		
1	1.17	(0.95, 1.44)	0.002
≥2	1.40	(1.15, 1.71)	
Proxy of performance status[d]			
ECOG 0-1	ref		0.41
ECOG 2-4	1.10	(0.88, 1.38)	
Prior autoimmune conditions[d]			
No	ref		0.51
Yes	1.07	(0.87, 1.31)	
Tumor Characteristics			
Stage at diagnosis			
I	ref		
II	1.12	(0.81, 1.55)	0.43
III	1.03	(0.83, 1.28)	
IV	0.92	(0.74, 1.14)	
Histology			
Non-squamous	ref		
Squamous	1.23	(1.05, 1.45)	0.04
NSCLC NOS	1.09	(0.84, 1.42)	
Central nervous system metastasis[d]			
No	ref		0.31

Yes	1.10	(0.91, 1.33)	
Treatment Characteristics			
Prior systemic therapy[e]			
Platinum doublets	ref		
None	1.04	(0.79, 1.38)	
Single chemotherapy	1.52	(1.06, 2.19)	0.01
Platinum doublets + bevacizumab	1.26	(1.00, 1.59)	
Other	1.31	(1.10, 1.56)	
Prior oral targeted therapy[f]			
No	ref		
Yes	1.01	(0.77, 1.31)	0.69
Unknown	1.07	(0.92, 1.25)	
Recent radiation[g]			
No	ref		0.001
Yes	1.47	(1.18, 1.83)	
Care at NCI-designated cancer center[h]			
No	ref		0.95
Yes	1.01	(0.84, 1.21)	
Time from diagnosis to initiation			
2 - 6 months	ref		
6 months - 1 year	0.83	(0.58, 1.18)	<0.001
1 - 3 years	0.64	(0.45, 0.91)	
>3 years	0.51	(0.35, 0.76)	

Abbreviation: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESRD, end-stage renal disease; HR, hazard ratio; NCI, National Cancer Institute; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; p, p-value; ref, reference group.

[a] Using the main cohort (n=1,256 patients). Of the 1,256 patients, 215 patients (17.12%) had an indicator of central nervous system metastasis.

[b] Results from a multivariable Cox proportional hazard model with all variables listed in the table. P values were calculated from Wald tests.

[c] Any state buy-in in the year prior to initiation.

[d] In the year prior to initiation.

[e] Since diagnosis. Includes chemotherapy and infusion targeted therapy. Excludes oral targeted therapy.

[f] Since diagnosis. Includes epidermal growth factor receptor tyrosine kinase (EGFR TKIs), anaplastic lymphoma kinase (ALK) and ROS1, BRAF and MEK inhibitors. Unknown status for those without continuous Medicare Part D coverage.

[g] In the 30 days prior to initiation.

[h] Defined as having any claim originating at a NCI-designated cancer center in the 90 days prior to initiation.

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Chapter 3 Appendix

[Appendix Methods 1] Patient selection criteria

Identifying recurrence

To identify patients who initiated first-line chemotherapy for recurrent breast cancer, we used the methods described in the prior literature.[1,2] For patients initially diagnosed with stage I-III breast cancer, we identified patients who received cancer-directed surgery within 4 months of cancer diagnosis from Medicare claims and the Patient Entitlement and Diagnosis Summary File (PEDSF). We then classified the periods following surgery as (1) initial treatment period that starts from the date of surgery, (2) treatment-free interval, and (3) surveillance period. For patients who did not receive any adjuvant chemotherapies within 4 months of initial surgery, initial treatment period was defined as 4 months after the date of surgery. For patients who received any adjuvant chemotherapy, the initial treatment period ends on the date of the last adjuvant chemotherapy claim. We used the same definition from prior literature to define the start and end date of adjuvant chemotherapy episode.[1] The treatment-free interval was defined as 90 days without any chemotherapy and radiotherapy claims following the end date of the initial treatment period. We additionally required 12 months chemotherapy-free interval based on the eligibility criteria of the randomized trial of bevacizumab.[3] Patients entered the surveillance period after the last date of treatment-free interval. We identified chemotherapy initiation during the surveillance period to determine first-line treatment for recurrent cancer.

Identifying human epidermal growth factor receptor 2 (HER2) status

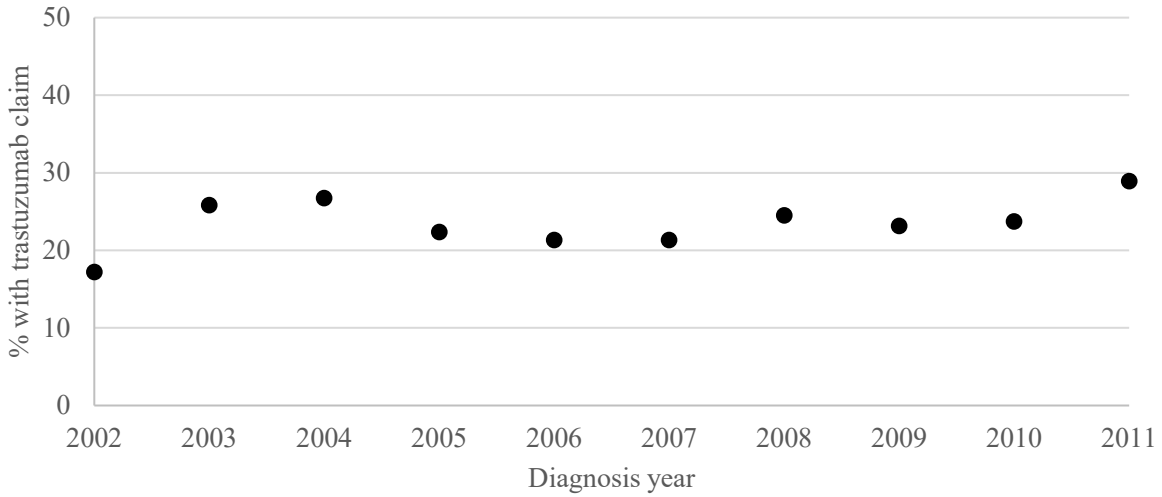
We used the presence of trastuzumab claim as a proxy of HER2 positive status for patients diagnosed between 2002 and 2009. HER2 status is highly associated with trastuzumab use among patients who initiate any systemic chemotherapy.[4] To examine the feasibility of this approach, we examined the presence of trastuzumab claims by HER2 status among patients diagnosed between 2010 and 2011 who initiated treatment for recurrent or metastatic breast cancer. Among 699 patients, HER2 status was highly associated with trastuzumab use as expected. 85.9% of patients without any trastuzumab claim was HER2 negative. 75.3% of patients with trastuzumab claim was HER2 positive. The percentage of patients with trastuzumab claims was also similar across diagnosis years. As most patients without trastuzumab claim between 2002 and 2009 will be HER2 negative, we used this variable as a proxy to select HER2 negative patients in our cohort selection process.

[Appendix Methods 1 – Table] Presence of trastuzumab claims by HER2 status among patients diagnosed between 2010 and 2011

	Trastuzumab		
n (%)	No	Yes	Total
Positive	NR	NR	159
Negative	444 (85.9)	27 (14.8)	471
Borderline	NR	NR	14
Unknown	41 (7.9)	14 (7.7)	55
	517	182	699

[Note] NR, not reported. Cell sizes of less than 11 were suppressed per NCI rules to preserve patient confidentiality. If a cell size of less than 11 can be extrapolated mathematically, we also suppressed the second smallest cell.

[Appendix Methods 1 – Figure 1] Percentage of patients with trastuzumab claims by diagnosis year



History of other primary cancer

For patients with recurrent breast cancer, we excluded those with history of any other primary cancer prior to chemotherapy initiation. We cannot determine whether the initiation of chemotherapy after the treatment-free interval is due to recurrent breast cancer or other cancers. For patients with metastatic breast cancer at diagnosis, we allowed patients with a history of prior cancer >5 years based on the criteria of randomized trials.[3,5]

[Appendix Methods 2] Statistical Analysis

We estimated pooled logistic regression models for overall survival in each treatment clone using time and baseline covariates. Using the predicted value in each clone, we obtained standardized survival probabilities, 1-year risk difference, and survival curves during the 156 weeks follow-up period. The results of pooled logistic regression models for overall survival in each clone are described in the following table.

[Appendix Methods 2 – Table 1] Parameter estimates from regression model for overall survival

	Fluoropyrimidine/Taxane only		Fluoropyrimidine/Taxane + Bevacizumab	
Variable	Coefficient	Standard error	Coefficient	Standard error
Intercept	-8.03	1.03	-4.44	2.34
Time in weeks	0.01	0.00	0.03	0.01
Time square	0.00	0.00	0.00	0.00
Age	0.06	0.01	0.00	0.03
Race (ref=white)				
Black race	-0.28	0.22	0.19	0.49
Other race	-0.44	0.24	1.56	0.52
State (ref=Washington)				
California/Hawaii	-0.30	0.26	0.14	0.78
Connecticut	0.10	0.32	-0.10	0.92
Georgia	-0.05	0.30	-0.03	0.80
Iowa	-0.57	0.38	0.95	0.85
Kentucky	-0.19	0.32	1.15	0.91
Louisiana	-0.14	0.33	0.60	0.84
Michigan	0.15	0.33	-0.13	1.02
New Jersey	-0.04	0.28	-0.66	0.81
New Mexico/Utah	-0.11	0.35	1.29	1.00
Less urban or rural (ref=metro or urban)	-0.04	0.21	0.06	0.45
Marital status (ref=widowed)				
Married	-0.17	0.13	-0.83	0.33
Other marital status	-0.14	0.15	-0.94	0.45
Medicaid dual eligibility (ref=no)	-0.03	0.17	0.36	0.45
Area-level poverty (ref=20% to 100% or unknown)				
0 to <5%	0.04	0.20	1.55	0.47
5 to <10%	-0.05	0.20	1.10	0.46
10 to <20%	0.07	0.19	0.47	0.44
# comorbid conditions (ref=3≤)				
0	-0.18	0.21	-1.14	0.58
1	-0.03	0.22	-1.82	0.66
2	0.08	0.26	-1.91	0.78
Poor performance status (ref=no)	0.55	0.18	-0.02	0.58
Stage at initial diagnosis (ref=IV)				

I	0.13	0.29	0.71	0.65
II	0.14	0.27	0.59	0.56
III	0.20	0.29	1.57	0.75
Grace at initial diagnosis (ref=not determined)				
I-II	-0.32	0.21	1.49	0.63
III-IV	0.24	0.21	1.72	0.65
ER status positive (ref=negative, borderline, unknown)	-0.11	0.14	-0.47	0.36
PR status positive (ref=negative, borderline, unknown)	-0.08	0.14	-0.14	0.36
Prior surgery (ref=mastectomy)				
None	-0.10	0.26	1.24	0.59
Breast conserving surgery	0.10	0.14	0.08	0.44
Prior adjuvant chemotherapy (ref=yes)	-0.41	0.13	-0.06	0.34
Prior radiotherapy (ref=yes)	0.06	0.13	-0.07	0.46
Chemotherapy regimen, fluoropyrimidines (ref=taxanes)	-0.27	0.11	-0.33	0.36
Flu vaccination (ref=yes)	0.08	0.11	-0.46	0.28
Care at NCI-designated cancer center (ref=no)	-0.04	0.18	0.20	0.49
# hospital admission (ref=2≤)				
0	-0.46	0.32	-2.10	0.74
1	-0.37	0.32	-1.54	0.74
# emergency room visit (ref=2≤)				
0	-0.39	0.21	-0.29	0.50
1	-0.06	0.21	0.00	0.53

Abbreviations: ER, estrogen-receptor; NCI, national cancer institute; PR, progesterone-receptor.

To account for the potential selection bias created by artificial censoring of cloned data, we used inverse probability of censoring weighting methods. In the original (un-cloned) data, we estimated two pooled logistic regression models for bevacizumab initiation at each interval during the grace period. We estimated (1) the model for the denominator of the weights using time, baseline covariates, and time-varying covariates and (2) the model for the numerator of the weights using time and baseline covariates. The results of these models are described in the following table.

[Appendix Methods 2 – Table 2] Parameter estimates from regression model for bevacizumab initiation during grace period

	Denominator		Numerator	
Variable	Coefficient	Standard error	Coefficient	Standard error
Intercept	5.29	2.14	5.26	2.13
Time in weeks	-2.38	0.36	-2.42	0.36
Age	-0.07	0.02	-0.07	0.02
Race (ref=white)				
Black race	-0.08	0.46	-0.07	0.46
Other race	0.38	0.49	0.40	0.49
State (ref=Washington)				

California/Hawaii	-0.18	0.57	-0.23	0.57
Connecticut	0.02	0.73	0.02	0.73
Georgia	0.82	0.59	0.81	0.59
Iowa	0.58	0.71	0.60	0.71
Kentucky	-0.69	0.69	-0.73	0.69
Louisiana	0.31	0.66	0.28	0.66
Michigan	-0.56	0.84	-0.63	0.84
New Jersey	-0.07	0.59	-0.08	0.59
New Mexico/Utah	-0.80	0.82	-0.78	0.82
Less urban or rural (ref=metro or urban)	-0.17	0.38	-0.16	0.38
Marital status (ref=widowed)				
Married	0.06	0.27	0.06	0.27
Other marital status	-0.40	0.36	-0.40	0.36
Medicaid dual eligibility (ref=no)	-0.49	0.42	-0.54	0.42
Area-level poverty (ref=20% to 100% or unknown)				
0 to <5%	0.33	0.40	0.32	0.40
5 to <10%	-0.09	0.41	-0.10	0.41
10 to <20%	-0.05	0.37	-0.06	0.37
# comorbid conditions (ref=3≤)				
0	0.49	0.54	0.49	0.54
1	0.20	0.56	0.20	0.56
2	0.37	0.63	0.38	0.63
Poor performance status (ref=no)	-0.27	0.46	-0.23	0.46
Stage at initial diagnosis (ref=IV)				
I	0.50	0.54	0.53	0.54
II	0.43	0.51	0.47	0.51
III	0.70	0.58	0.75	0.58
Grace at initial diagnosis (ref=not determined)				
I-II	-0.29	0.44	-0.35	0.44
III-IV	-0.08	0.44	-0.14	0.43
ER status positive (ref=negative, borderline, unknown)	-0.11	0.32	-0.11	0.32
PR status positive (ref=negative, borderline, unknown)	0.10	0.30	0.11	0.30
Prior surgery (ref=mastectomy)				
None	-0.82	0.50	-0.81	0.50
Breast conserving surgery	-0.13	0.30	-0.10	0.30
Prior adjuvant chemotherapy (ref=yes)	0.38	0.29	0.38	0.29
Prior radiotherapy (ref=yes)	0.29	0.31	0.29	0.31
Chemotherapy regimen, fluoropyrimidines (ref=taxanes)	0.00	0.24	0.01	0.24
Flu vaccination (ref=yes)	-1.65	0.30	-1.64	0.30
Care at NCI-designated cancer center (ref=no)	-0.17	0.53	-0.51	0.43
# hospital admission (ref=2≤)				
0	-0.27	0.70	-0.37	0.70
1	0.04	0.68	-0.04	0.68
# emergency room visit (ref=2≤)				
0	0.69	0.52	0.85	0.51

1	0.76	0.52	0.88	0.52
NCI cancer center use in the previous week	-0.93	0.92	-	-
Emergency room visit in the previous week	-1.04	1.09		

Abbreviations: ER, estrogen-receptor; NCI, national cancer institute; PR, progesterone-receptor.

We used the predicted values in Table 2 to create stabilized weights in the cloned data. Table 3 describes the construction of the weights in each time interval (week). A_k is an indicator of bevacizumab initiation at week *k*, L_0 is the vector of baseline covariates, and L_k is the vector of time-varying covariates. Using these weights, we weighted each observation in the cloned data when estimating overall survival. Censored individuals in each interval were assigned a weight of 0.

[Appendix Methods 2 – Table 3] Construction of inverse probability weights

	Fluoropyrimidine/Taxane only	Fluoropyrimidine/Taxane + Bevacizumab
t=1	$\prod_{k=1}^{t} \frac{(1 - f(A_k \mid \overline{A_{k-1}} = 0, L_0))}{(1 - f(A_k \mid \overline{A_{k-1}} = 0, L_0, L_k))}$	1
t=2		$\frac{f(A_k \mid \overline{A_{k-1}} = 0, L_0)}{f(A_k \mid \overline{A_{k-1}} = 0, L_0, L_k)}$
t≥3	Weights from t=2 carried forward	

[Appendix Table 1] Code definitions for study variables

Variables	Codes
Cancer-directed surgery[a]	
Breast conserving surgery	ICD-9: 8520, 8521, 8522, 8523, 8524, 8525 CPT: 19120, 19125, 19126, 19160, 19162, 19301, 19302
Mastectomy	ICD-9: 8534, 8536, 8540, 8541, 8542, 8543, 8544, 8545, 8546, 8547, 8548 CPT: 19180, 19182, 19200, 19220, 19240, 19303, 19304, 19305, 19306, 19307
Chemotherapy and targeted therapy	
Bevacizumab	HCPCS: J9035, S0116, Q2024, C9257, C9214 Excluded ophthalmic use based on the following CPT and principal diagnosis codes CPT: 67028 ICD-9: 36250, 36251, 36252 25050, 36207, 36202, 25051, 25052, 36201, 25000, 36236, 36235
5-Fluorouracil	HCPCS: J9190
Capecitabine	HCPCS: J8520, J8521 NDC: 51407009612, 69097094808, 69539002092, 69539002099, 69539001960, 69539001999, 51407009560, 51079051005, 42291016712, 72205000660, 16714046701, 16714046801, 00179014970, 00179019570, 00179022970, 00378251191, 00378251278, 67877045812, 67877045830, 67877045860, 60687014994, 69097094903, 65162084306, 65162084406, 65162084416, 65162084450, 50268015413, 42291016660, 59651020508, 59651020510, 59651020410, 72205000792, 59651020460, 00054027121, 00054027223, 16729007212, 16729007329, 67877045912, 67877045930, 67877045960, 63759030001, 63759030011, 64980027606, 64980027712, 00093747306, 00093747489, 00004110020, 00004110150, 00004110116, 00004110051, 00004110013, 00004110022, 00004110113, 00004110151, 00004110175
Paclitaxel	HCPCS: J9264, J9265, J9267 C9127, C9431
Docetacel	HCPCS: J9170, J9171
Trastuzumab	HCPCS: J9355, J9354, C9131
Doxorubicin	HCPCS: J9000, J9001, J9002, Q2050, Q2048, Q2049, C9415
Carboplatin	HCPCS: J9045
Cyclophosphamide	HCPCS: J8530, J9093, J9070, J9080, J9090, J9092, J9095, J9091, J9094, J9096, J9097, C9420, C9421 NDC: 00015050301, 00015050302, 00015050401, 00054412925, 00054413025, 00054808925, 00054813025
Methotrexate	HCPCS: J9250, J9260, J8610
Vinorelbine	HCPCS: J9390, C9440
Epirubicin	HCPCS: J9178, J9180
Gemcitabine	HCPCS: J9201
Cisplatin	HCPCS: J9062, J9060, C9418
Irinotecan	HCPCS: J9206, C9474, J9205
Radiotherapy	ICD-9-diagnosis: V580, V661, V671 ICD-9-procedure: 9221, 9222, 9223, 9224, 9225, 9226, 9228, 9229 CPT: 77261, 77262, 77263, 77280, 77285, 77290, 77293, 77295, 77299, 77300, 77301, 77305, 77310, 77315, 77321, 77326, 77327, 77328, 77331, 77332, 77333, 77334, 77336, 77338, 77370, 77371, 77372, 77373, 77399, 77401, 77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416, 77417, 77418, 77421, 77423, 77424, 77425, 77427, 77431, 77432, 77435, 77470, 77471, 77499, 77520,

	77522, 77523, 77525, 77750, 77761, 77762, 77763, 77776, 77777, 77778, 77781, 77782, 77783, 77784, 77785, 77786, 77787, 77789, 77790, 77799 Revenue center code: 0330, 0333
Secondary malignant neoplasm of brain and spinal cord	ICD-9-CM: 1983 Also used the variable available in the Patient Entitlement and Diagnosis Summary File.
Charlson comorbid conditions[b]	Used the SAS macro available from the National Cancer Institute Division of Cancer Control & Population Science (Macro updated date: 03/24/2017)
Contraindications for bevacizumab[c,6]	
Cardiac disease	ICD-9 diagnosis: 410, 411, 4275, 428, 4297 ICD-9 procedure: 3794, 3795, 3796, 3797, 3798, 3961, 3962, 3963, 3965, 3966, 360, 376 CPT: 33510−33548, 33960−33980, 33983, 33572, 93508−93524
Thrombosis	ICD-9 diagnosis: 4151, 41511, 41519, 452, 444, 4440, 4441, 44421, 44422, 4448, 44481, 44489, 4449, 445, 4450, 44501, 44502, 4458, 44581, 44589, 453 CPT: 34401, 34421, 34451, 34471, 34490, 34001, 34051, 34101, 34111, 34151, 34201, 34203
Hemorrhage	ICD-9 diagnosis: 4230, 431, 4329, 44621, 4590, 53082, 53789, 56881, 5789, 7827, 7847 CPT: 49002, 46614, 52606, 32654, 44391, 45382, 45317, 45334, 43227, 43255, 44366, 44378, 47350, 32110, 31238, 59160, 57180, 30901, 30902, 30903, 30904, 30905, 30906, 42970, 42971, 42972, 42960, 42961, 42962
Hemoptysis	ICD-9 diagnosis: 7863
Stroke	ICD-9 diagnosis: 43491, 43401, 43411, 433
GI perforation	ICD-9 diagnosis: 56983, 5304, 5307, 5311, 5312, 5315, 5316, 5321, 5322, 5325, 5326, 5331, 5332, 5335, 5336, 5341, 5342, 5345, 5346 CPT: 43501
Major surgical procedure in the past 28 days	Used the Surgery Flags Software version 1.1 by the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HCUP)
Hormone therapy	
Letrozole	GNN variable used
Anastroole	GNN variable used
Exemestane	GNN variable used
Tamoxifen	GNN variable used
Fulvestrant	HCPCS: J9395
Emergency room visit	Revenue center codes: 0450-0459, 0981 Emergency room charge amount variable in MedPAR file
Flu vaccination[b]	HCPCS: G0008, Q2034-Q2039 CPT: 90630, 90682, 90724, 90756, 90653-90662, 90672-90674, 90685-90688

Abbreviations: CPT, Current Procedural Terminology; GNN, generic name; HCPCS, Healthcare Common Procedure Coding System; ICD, International Statistical Classification of Diseases; NDC, National Drug Code.

[a] Surgery information in the SEER PEDSF file was also used.

[b] During the year prior to treatment initiation.

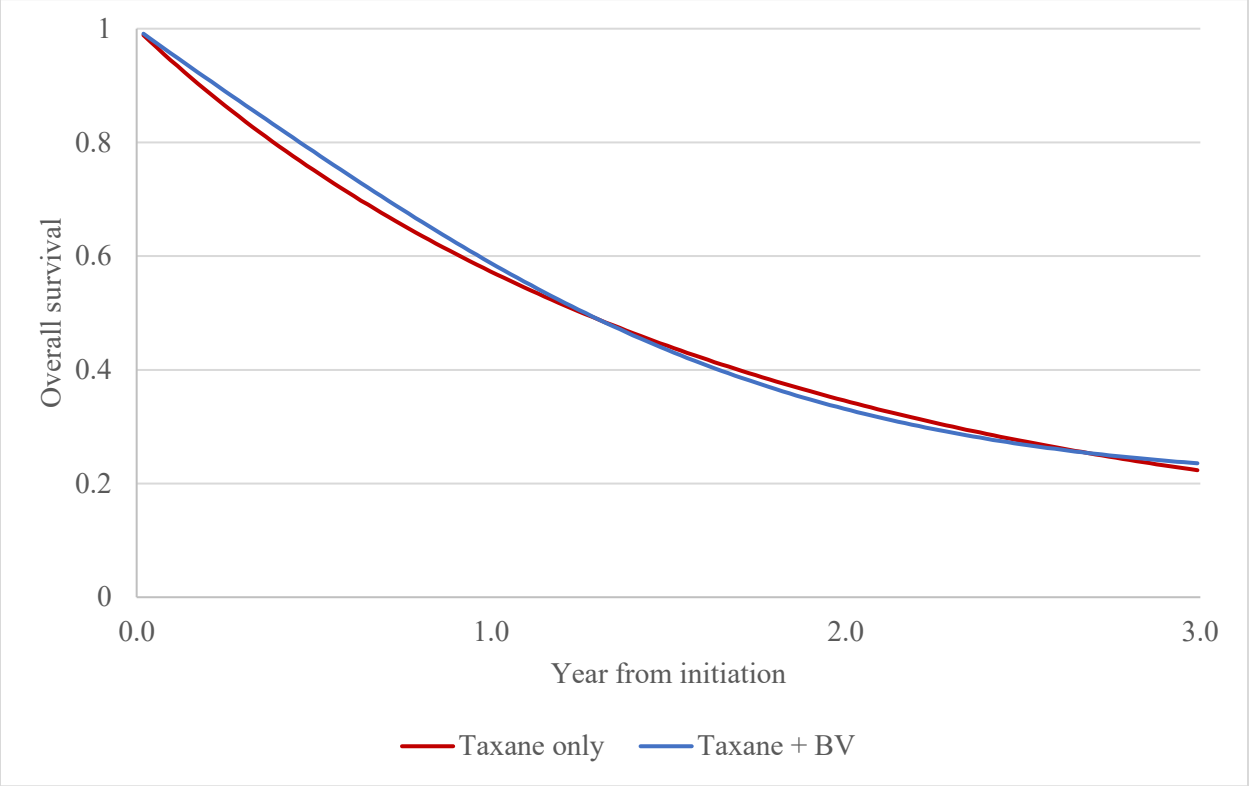
[c] at least one claim from inpatient file or at least two claims on separate dates. During the 6 months prior to treatment initiation.

[Appendix Table 2] Comparison of patients in the SEER-Medicare analysis and randomized trials

	SEER-Medicare	AVADO			RIBOON-1			
	All patients	Docetaxel + PL	Docetaxel + BV low dose	Docetaxel + BV high dose	Cape +PL	Cape +BV	Tax/Anthra + PL	Tax/Anthra +BV
n	649	241	248	247	206	409	207	415
Age, years								
Median	77	55	54	55	57	56	55	55
Range	66-96	29-83	26-83	27-76	23-88	28-91	29-85	28-88
≥65, %	-	16	17	19	-	-	-	-
Prior therapy								
Surgery	77	-	-	-	91	89	76	77
Adjuvant chemotherapy*	36	65	65	68	76	70	47	45

Abbreviations: Anthra, anthracycline; BV, bevacizumab; Cape, capecitabine; PL, placebo; Tax, taxanes.

[Appendix Figure 1] Overall survival of subgroup of patients who initiated taxane as their standard chemotherapy



[Abbreviations] BV, bevacizumab.

1-year risk difference: 1.5% (95% CI: -7.5, 13.0); Hazard ratio: 0.95 (95% CI: 0.75, 1.25); n=389.

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