ACCESSIBILITY AND AFFORDABILITY OF HIGH PRICED DRUGS IN ADVANCED NON-SMALL CELL LUNG CANCER

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ABSTRACT

Yi-Ting Chou: Accessibility and affordability of high priced drugs in lung cancer
(Under the direction of Stacie Dusetzina)

Lung cancer is the leading cause of cancer death in the U.S. It is a disease with poor prognosis that mainly occurring in older population. Treatment options have been increasing for lung cancer recently. However, high out-of-pocket costs is a major concern regarding the use of novel drug treatments, which could impact patient's choice of treatment and even poorer patient outcomes in the long term. Among all, health insurance is an important modifier of financial burden. The study objectives were to examine the extent of Medicare's benefit designs for drug treatments and the effect of cost-sharing support on treatment uptake in advanced non-small cell lung cancer (NSCLC).

We first used Medicare plan formulary files to evaluate the changes in drug prices and benefit designs for lung cancer medications. We then used the SEER-Medicare databases to examine drug utilization, key factors associate with the use through modified Poisson regression, and the effect of cost-sharing support through low-income subsidy on the timing of treatment initiation in the advanced NSCLC population through multivariable COX proportional hazards regression and propensity score weighting.

We observed higher entry prices at FDA approval overtime in Part D advanced NSCLC drugs while considerable price hike was also found in older drugs. In addition, high adoption rates of specialty/top tier and utilization management tools were found among Part D plans and across treatment options. The use of Part D medications has been stable but lower than expected.

Particularly, we found that low-income subsidy served as a critical factor for Part D drug use and timely initiation of Part D treatment among the advanced NSCLC population.

With current plan benefits and ever-increasing drug prices, concerns over affordability of and accessibility to Part D treatments could continue for advanced NSCLC patients. Patient out-of-pocket costs could particularly present a considerable barrier to timely treatment initiation. In the context of current evolving health care reform, identifying sustainable strategies to improve patient affordability of and equal access to high quality care are needed for the cancer population.

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LIST OF ABBREVIATIONS

ALK	Anaplastic lymphoma kinase
DS	Disability Status
EGFR	Epidermal growth factor receptor
HR	Hazard Ratio
IPTW	Inverse probability of treatment weighting
LIS	Low-income subsidy
NSCLC	Non-small cell lung cancer
PA	Prior authorization
PS	Propensity Score
QL	Quantity limit
RR	Risk ratio / relative risk
SEER	Surveillance, Epidemiology, and End Results
ST	Step therapy

CHAPTER ONE: INTRODUCTION

1.1 OVERVIEW

Lung cancer is the leading cause of death from cancer and the second most common cancer among both men and women in the United States (U.S.).[1,2] In 2017, an estimated 222,500 new cases of lung cancer are expected to be diagnosed and 155,870 patients will die from the disease, representing 13% of all new cancers and more than one-fourth of all cancer death, respectively.[1,2] Lung cancer is a disease mainly occurring among older populations with an average age of 70 at the time of diagnosis.[3] More than 80% of patients are diagnosed at stages III and IV with 5-year survival of only 4.2% for those with stage IV disease.[1–3] Due to the high mortality of the disease, there is a significant need for treatments that extend survival for these patients.

Until recently, treatments available to lung cancer patients were limited. For late stage cancer, chemotherapy has been the main treatment. However, advances have been made in pharmaceutical discovery, research, and development in recent years. Since 2010, 14 cancer drugs (12 new drugs and 2 older drugs with new indications) have been approved by the United States Food and Drug Administration (FDA) for lung cancer, all of which are biological targeted therapies.[4] These novel targeted therapies are increasing the number of treatment options for patients and are generally preferred over traditional anticancer therapies (chemotherapy) due to greater clinical efficacy, lower rate of severe adverse events, and improved outcomes in quality

of life and/or symptom assessments.[5,6] According to a 2015 marketing report, there are currently 661 lung cancer drugs under development targeting 377 different gene mutations; 49 of these have entered phase III trials.[7] Further, recent success in immunotherapy trials suggest that research and development focused on lung cancer is expected to increase.[6]

A major concern regarding the use of targeted treatments is their high cost to both patients and society. On average, the monthly cost of these novel drugs for lung cancer in the U.S. is $9,945 (in 2014 US dollars) with a range from $2,069 (gefitinib, Iressa®) to $14,837 (atezolizumab Tecentriq®)[8], with prices doubling in the last decade.[6,9] In addition, cancer regimens increasingly consist of multiple drugs (either sequential or combination therapies), which exacerbates the cost problem.[10] Prior research has found that patients going through cancer treatments can be burdened with high out-of-pocket costs, termed "financial toxicity".[11–13] The resulting financial distress, and even bankruptcy following cancer diagnosis [14–16], has been reported to impact patient's choice of treatment and adherence to therapy, [17–19] leading to poorer patient outcomes,[20,21] reduced quality of life,[22,23] and even greater costs of care in the long term.[20]

However, a major modifier of financial burden is health insurance. In the context of lung cancer treatment, Medicare is a primary payer – largely due to the age of patients needing treatment. Under the federal Medicare program, which provides health insurance coverage for individuals aged 65 years or older, the cost of drug treatments can be covered through either the outpatient medical benefit (Part B) or the outpatient pharmacy benefit (Part D).[24] This distinction is important because coverage varies between Medicare Part B and Part D and affects the level of expected out-of-pocket spending required for patients needing different types of anticancer drugs.

Medicare Part B, as part of traditional / fee-for-service Medicare (i.e., the Original Medicare), is administered directly through the federal government. It applies a standardized coverage structure for services included in the program, including injectable and infused drugs that are not usually self-administered and that are furnished and administered as part of a physician service. In 2017, for example, in addition to a standard monthly premium, patients with Part B pay a deductible (on average $183) and/or coinsurance when receiving health services (usually 20% of the Medicare-approved cost for outpatient care).[25] Despite the above cost-sharing requirements under Part B, there are supplemental health insurance options available for beneficiaries to fully or partially pay those cost-sharing requirements, including deductibles, copayments, and coinsurance. According to Kaiser Family Foundation, more than 80% of fee-for-service Medicare beneficiaries have some source of coverage that supplements Medicare, including Medigap, employer or union-sponsored retiree health plans, and Medicaid for individuals with low-incomes.[26,27] This supplemental coverage results in more consistent and predictable expenses for patients using Part B services throughout the year.

In contrast, Medicare Part D, the outpatient prescription drug benefit for most orally-administered anticancer medications, is offered through private insurance companies. Because of this, the cost-sharing requirement for drug treatments varies across plans (although plans are required to be actuarially equivalent to a prescribed standard benefit package). According to the Centers for Medicare & Medicaid Services (CMS), the Part D base beneficiary premium in 2017 is $35.63, with adjustment by income. In 2017, the Part D standard benefit has a $400 deductible and 25% coinsurance up to an initial coverage limit of $3,700 in total drug costs, followed by a coverage gap, in which a beneficiary pays 40% of their prescription costs (100% patient responsibility before 2011), until the cost reaches the catastrophic coverage threshold of $8,071

in drug costs.[25] After entering the catastrophic coverage phase, Part D enrollees pay 5% of the drug price (or $3.30 for generics or $8.25 for brand-name drugs, whichever is greater) for covered drugs for the rest of the year.[25] For medications offered on Part D there has been increasing use of coinsurance (where the patient pays a percentage of the drug's price) over time.[28–30] Given the high price of novel anticancer medications, patients obtaining these drugs through their Medicare Part D plans are expected to face significant out-of-pocket spending.

In addition to standard cost-sharing structures, to limit the use of expensive therapies, Medicare Part D plan sponsors may also adopt restrictive formularies and engage utilization management tools. [28,30,31] Formulary structures consist of drug tier placement and cost-sharing amounts assigned to these tiers (through copayments or coinsurance arrangements). Typically, higher tier placement requires greater patient cost-sharing for the drug. Prescription drug benefits typically include at least three tiers: Tier 1 for generic drugs, Tier 2 for preferred brand-name drugs, and Tier 3 for non-preferred brand-name drugs. In recent years, there has been an increase in both plan use of tiering and the number of tiers in a formulary, specifically including a unique specialty drug tier.[30,32] Specialty drug tiers often include high-priced treatments; those typically used for complex conditions including cancer.[33,34] The growth of specialty tiering in outpatient drug formularies reflects plans' attempts to contain costs.

Although cancer drugs are required to be included on Part D plan formularies due to their status as a protected drugs, many are placed on specialty tiers that require patients to pay a percentage of the drug price (i.e., coinsurance) rather than a fixed dollar amount (i.e., copayment).[35] As a result, a patient filling an anticancer drug on Medicare Part D can face thousands of dollars in annual out-of-pocket costs.[36]

In addition to tiered cost sharing, utilization management tools may be employed to

enforce formulary adherence or to manage drug costs for Part D payers more generally.[31] These measures include prior authorization (i.e., the plan must grant permission before a particular drug can be prescribed and qualified for coverage), quantity limits (i.e., restriction on the amount of drugs a plan will cover over a certain period of time) and step therapy (i.e., use less expensive drug options before "stepping up" to treatments that cost more). If utilization restrictions are not met, a patient would have to pay out-of-pocket for using the drug despite the fact that the drug is listed on the formulary by his/her plan. Drugs in higher tiers or specialty drugs are regularly subject to utilization management requirements.[36] Although these interventions are effective cost-management tools for payers, they can affect appropriate access to care and thus treatment utilization for patients.[31]

Affordability of and patient access to care are major issues in cancer care.[37–41] Compared to traditional chemotherapies offered through Medicare Part B, patients might face greater barriers to accessing drugs offered under Part D due to the plan's benefit structure and the relative lack of out-of-pocket cost protections that are typically available for drugs offered under Part B. For those who are newly diagnosed with cancer, initial access to treatment is particularly important as prompt treatment is often essential. However, for Medicare beneficiaries needing orally-administered anticancer therapies covered under their prescription drug benefit (Part D) to initiate the treatments, they may be responsible for very high out-of-pocket spending given plan's benefit designs and limited support of out-of-pocket cost. This high up-front cost for initiating anticancer treatment could cause delay in obtaining appropriate care. One key exception to this exists for Medicare Part D enrollees who are eligible and enrolled in the Low-Income Subsidy (LIS) program.[42,43] This program provides patients with cost-sharing support for Part D prescription drugs but is only available to Medicare beneficiaries with limited income (≤

150% federal poverty level) and resources (≤ $12,320 for individuals in 2017). [42,43] For a full-subsidy qualified individual, he/she is exempt from the monthly premium, annual deductible, and has no cost-sharing during the coverage gap or above the annual out-of-pocket catastrophic coverage threshold. In addition, all Part D plans are required to charge full LIS beneficiaries the same fixed copayment amounts rather than coinsurance for drugs that they fill. For example, in 2017, patients with full LIS are responsible for no more than $3.30 for each generic or $8.25 for each brand-name covered drug. In contrast, those without full LIS assistance could face coinsurance from 5-51% of the drug's price depending on the coverage phase and the type of drug used. According to CMS, average patient out-of-pocket costs of using a Part D drug during a year could be more than a hundred times higher for beneficiaries without versus with a LIS.[44] In 2016, over 12 million beneficiaries (28.9% of Part D enrollees) are receiving drug coverage for little or no cost through LIS.[45,46] In the context of anticancer therapies, having the subsidy could mean a difference of thousands of dollars out-of-pocket for patients using the same drug, even for just the first prescription fill.[36,47]

Lung cancer is currently one of the top five most expensive cancers nationwide and accounts for the largest proportion (13%) of cancer-related expenditures in Medicare among all cancer types.[48] It is estimated that approximately 13% of total Medicare expenditures for lung cancer care is paid directly out-of-pocket by patients.[48] With a number of targeted therapies for lung cancer emerging on the market combined with high drug prices and the aging of the U.S. population, the economic burden of lung cancer will be considerable and will likely increase significantly in coming years. Given health plans' efforts to contain costs, this may result in greater cost shifting from plans to patients over time.

To date, the extent of health insurance coverage for drug treatments has not been explored from a disease-specific perspective. This is particularly crucial for lung cancer as high-priced novel drugs have been increasingly approved for the disease over time and are expected to grow in the near future. Understanding the scope of coverage provided for lung cancer drug treatment options and the effect of cost-sharing support on treatment uptake could provide insights into treatment affordability and accessibility among patients with NSCLC, improve clinical decision making, as well as inform policy movement towards affordable and equal access to high quality care for the cancer population.

1.2 SPECIFIC AIMS AND HYPOTHESIS

I propose to evaluate the accessibility and affordability of anticancer medications used to treat advanced non-small cell lung cancer (NSCLC), which accounts for more than 85% of lung cancer cases. I focus on drug-specific price and formulary structure and utilization management tools applied for advanced NSCLC medications covered by Medicare Part D (Aim#1), available treatment options for advanced NSCLC and their real-world utilization through Medicare Part B and Part D coverage (Aim#2), as well as the effect of Medicare Part D low-income subsidy on treatment uptake (Aim#3).

To achieve these goals, Aim 1 was conducted using the Medicare Prescription Drug Plan Formulary, Pharmacy Network, and Pricing Information Files. Given the up-to-date availability of the data, the examination expands the number of treatments studied to include those approved by June 2017. Aims 2 and 3 both utilize the SEER-Medicare linked databases, with the latest available data, including patients diagnosed with cancer by the end of 2013 and their fee-for-service Medicare claims through 2014. The specific aims are as follows:

Specific Aim 1: Examine changes in drug-specific prices, formulary structure, and the use of utilization management tools for Part D medications approved for advanced NSCLC from 2009 to 2017.

Hypothesis 1a: Over time Part D drug prices have increased over the study period in addition to inflation.

Hypothesis 1b: Over time advanced NSCLC medications covered under Part D are more likely to be placed on the highest drug tier or specialty drug tier within the formulary.

Hypothesis 1c: Over time advanced NSCLC medications covered under Part D are more likely to require coinsurance (rather than copayments) for calculating patient cost-sharing.

Hypothesis 1d: Over time advanced NSCLC medications covered under Part D are more likely to be subject to utilization management (e.g., step therapy, prior authorization, quantity limits).

Proposed Contribution to the Literature: Formulary structure and associated benefit design within Medicare Part D plans for anticancer medications have not been examined specifically in advanced NSCLC settings. This exploration is expected to provide insights into the level of coverage for novel advanced NSCLC treatments to inform the scope of patient responsibility for treatment cost (i.e., treatment affordability) in NSCLC care.

Specific Aim 2: To examine trends in the utilization of advanced NSCLC medications by coverage source (i.e., Medicare Part B or Part D). In addition, to identify clinical, sociodemographic, and health system factors associated with the use of Part D treatments among patients diagnosed with advanced NSCLC from 2007 to 2014.

Hypothesis 2a: The use of advanced NSCLC medications covered under Part D has increased over the study period.

Hypothesis 2b: The use of advanced NSCLC medications covered under Part B has decreased over the study period

Proposed Contribution to the Literature: Real-world utilization of treatments for advanced NSCLC care remains largely unknown and may vary by coverage source. Particularly, how novel therapies have been adopted over recent years and the characteristics of patients receiving orally-administered therapies covered under Part D has not been previously explored. The examination will promote better understanding of differential patient access to treatment under the effects of price, plan benefit design, and reimbursement policies assigned to the drug treatments, which could be targets for policy intervention.

Specific Aim 3: Evaluate the effect of low-income subsidies for Medicare Part D medications on treatment initiation among patients with advanced NSCLC from 2007 to 2014.

Hypothesis 3a: For medications covered under Part D, due to the higher cost-sharing required for patients who do not receive low income subsidies, time to initiation is shorter among patients with (full or partial) low-income subsidies as compared to those without.

Hypothesis 3b: For medications covered under Part B, due to the availability of supplemental insurance coverage for reducing or eliminating out-of-pocket costs for most Medicare enrollees, there is no difference in the time to initiation among patients with low-income subsidies as compared to those without.

Proposed Contribution to the Literature: There is limited evidence regarding the impact of high up-front cost sharing on patient access to drugs offered on Medicare Part D. By comparing time to initiation of orally-administered anticancer drugs for patients with and without a low-income subsidy, we will gain insight into cost-related barriers to treatment use in an advanced NSCLC population. This examination may inform policy movement towards affordable and equal access to high quality care for the cancer population.

1.3 SIGNIFICANCE AND INNOVATION

For understanding treatment access and affordability in the context of advanced NSCLC, we will examine changes in drug-specific price and formulary structures and utilization management tools applied by Medicare Part D plans, examine the trends in real-world medication use by coverage source (i.e., Medicare Part B or Part D), and estimate the effect of low-income subsidies for Medicare Part D medications on treatment initiation.

The study is innovative in many aspects. First, distinct from general overview of drug coverage in the U.S., our examination applies a disease-specific perspective for understanding the scope of care affordability and accessibility in a population with significant unmet needs. Beyond focusing on drug prices alone, our planned approach also considers diverse angles of growing patient financial burden in cancer care, including the benefit structure of plans as well as financial assistance in prescription drug expenses through the Medicare part D low income subsidy program. In addition, we examine the role of cost-sharing subsidies on treatment initiation to identify possible gaps in treatment access – a crucial element to optimizing cancer care, particularly in advanced cancer settings. To our knowledge, this project is the first study to examine the drug coverage and resulting patient cost-sharing on high-priced novel anticancer

drugs as well as the corresponding effect on treatment uptake among the advanced NSCLC population.

This study will contribute to an in-depth understanding of the Medicare beneficiary out-of-pocket costs for currently available lung cancer treatment options and the effect of cost-sharing support for out-of-pocket costs on access to treatment. This information could be used to improve physician-patient discussions around challenges to obtaining novel orally-administered cancer treatments and may inform policy decisions around increasing affordability and accessibility of cancer medications for the population.

CHAPTER TWO: LITERATURE REVIEW

2.1 Advanced Non-Small Cell Lung Cancer Overview

2.1.1 Epidemiology

Lung cancer is the leading cause of death from cancer and the second most common cancer among both men and women in the United States (U.S.). [1,2] In 2017, an estimated 222,500 new cases of lung cancer are expected to be diagnosed and 155,870 patients will die from the disease, representing 13% of all new cancers and more than one-fourth of all cancer death, respectively.[1,2] Among three main types of lung cancer, non-small cell lung cancer (NSCLC) is the most common type, accounting for about 85% of cases.[1,3] The average patient age at diagnosis is around 70 years old.[3] Due to lack of salient symptoms in its early stage, the disease is mostly diagnosed at late stages.[1–3,49] More than 80% of patients present with stage III or IV disease at the time of diagnosis, and the five-year survival is usually poor at less than 5% for those with distant-stage diseases.[1–3,49]

Smoking is the main cause of lung cancer. Approximately 85-90% of cases are caused by voluntarily or involuntary (second-hand) cigarette smoking.[1,50,51] While smokers are 15 to 30 times more likely to develop lung cancer or die from lung cancer than nonsmokers,[52] recent epidemiological data of increased rates of NSCLC among never smokers suggest specific molecular and genetic tumor characteristics could also be related.[53] Other known risk factors also include sex, family history, previous cancer history, occupational exposure, other lung disease, exposure to infectious agents, exposure to chemicals, or history suggestive of infection.[1,50–52]

Patients with NSCLC experience high symptom burden and reduced quality of life throughout the course of NSCLC diagnosis and treatment.[54,55] The most common symptoms associated with NSCLC are dyspnea, pain, fatigue, and coughing, which are especially prevalent in advanced disease and adversely impact patient health-related quality of life (HRQoL).[1,54] For example, the mean utility score of quality of life ranged from 0.62 to 0.75 for advanced NSCLC (the value assigned represents a year of healthy life expectancy, with ranges from 0.0 for being dead up to 1.0 for living in perfect health).[54–59] A U.S.-based multicenter study on advanced at 11 tumor sites showed the lowest HRQoL score in lung cancer and that it is significantly associated with pain/discomfort and difficulty in performing usual activities for patients.[60] Even with treatment, disease progression and severe adverse events were reported to have a considerable negative impact on HRQoL, scores low at 0.46 and 0.52, respectively.[54–59] This stresses the importance of developing treatments that improve survival as well as reduce disease progression and severe toxicities for advanced NSCLC.

2.1.2 Treatment options

Prior to 2010, treatments available to advanced NSCLC patients were limited. For locally advanced or metastatic disease (stage IIIB/stage IV) drug regimens were typically limited to chemotherapy, depending on the patient's overall health.[50,51] Platinum-based chemotherapy has been considered the standard-of-care, particularly for patients with unknown genetic status.[50,51,61]It has been shown to prolong survival, improve symptom control, and it yields superior quality of life compared to best supportive care.[62] Data from randomized controlled trials suggest that combinations of platinum-based chemotherapy with newer agents (e.g., cisplatin/gemcitabine and cisplatin/pemetrexed) have generated a plateau in overall response

rates (25%–35%), time to progression (4–6 months), median survival time (8–10 months), 1-year survival rate (30%–40%), and 2-year survival rate (10%–15%) in fit patients (e.g., at least being capable of all selfcare or performance status score 0-2).[51] The suboptimal efficacy and considerable toxicity of chemotherapy underscored the unmet patient needs in advanced NSCLC care, as only a small impact on survival was observed.

Advances have been made in pharmaceutical discovery, research, and development in recent years. Histology and gene mutation have been found to be of importance in the management of NSCLC.[51,61] Particularly, the discovery of actionable molecular abnormalities from the early 2000s, such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), have led to a major shift in the treatment paradigm.[61,63–65] Until recently, immunotherapy for lung cancer has become a burgeoning revolutionized therapeutic modality.[6,66–69] Randomized trial data have shown that immunotherapy can greatly improve median survival (9-17 months), overall response rate (17-30%), 1-year survival rate (42-56%), and 2-year survival (24-40%) as compared to traditional chemotherapy in fit patients.[66] These novel targeted therapies are expected to be less toxic than traditional chemotherapies because they can make distinctions between cancerous and normal cells, targeting the cancer cells directly or through stimulating a patient's own immune system to recognize cancer cells more effectively without damaging normal healthy cells, which pushes the boundary to significantly improve patient outcomes and quality of life.[5] Therefore, these novel targeted therapies are generally preferred over traditional chemotherapy.[6] Not only do the targeted therapies increase the number of treatment options for patients, it also allows for a more tailored selection of treatment in advanced NSCLC care.[6,51]

Since 2010, 14 cancer drugs (12 new drugs and 2 older drugs with new indications) have been approved by the United States Food and Drug Administration (FDA) for lung cancer, all of which are biological targeted therapies.[4] To date, types of targeted drugs available include

1) Monoclonal antibodies targeting tumor blood vessel growth (e.g., bevacizumab (Avastin®), ramucirumab (Cyramza®)) (IV therapies)
2) Monoclonal antibody targeting EGFR (e.g., necitumumab (Portrazza®)) (IV therapies)
3) EGFR tyrosine kinase inhibitors (e.g., erlotinib (Tarceva®), afatinib (Gilotrif®), gefitinib (Iressa®), osimertinib (Tagrisso®)) (oral therapies)
4) ALK tyrosine kinase inhibitors (e.g., crizotinib (Xalkori®), ceritinib (Zykadia®), alectinib (Alecensa®), brigatinib (Alunbrig®)) (oral therapies)
5) Immunotherapy with PD-1/PD-L1 inhibitors (i.e., nivolumab (Opdivo®), pembrolizumab (Keytruda®), atezolizumab (Tecentriq®) (IV therapies)

Recent success in immunotherapy trials suggest that research and development focused on lung cancer is expected to increase in the near future for both monotherapy and combination treatments.[6,70]

2.2 Treatment Burden of Medicare Beneficiaries with Advanced NSCLC

2.2.1 High cost of novel treatments

A major concern regarding the use of novel treatments is their high cost to both patients and society.[71] In 2015, U.S. national health expenditure increased 5.8% to reach $3.2 trillion, or $9,990 per person. Among different types health spending, prescription drug spending outpaced all other services in 2015 and has grown to account for 10.1% of all health spending.[72] The

strong spending growth for prescription drugs is attributed to the increased spending on new medicines, price growth for existing brand name drugs, increased spending on generics, and fewer expensive blockbuster drugs going off-patent.[72,73] For Medicare specifically, spending on Part B drugs (usually injectable or infused drugs) — a category dominated by drugs used to treat cancer — doubled from $13 billion in 2009 and to $26 billion in 2015.[74] Similarly, spending on Part D drugs increased from $46 billion in 2007 to over $80 billion in 2015 (an average annual growth rate of more than 7%).[74]

The strong upward rise in specialty drug prices and availability, including cancer drugs, has contributed to Medicare's spending growth.[72–74] According to a National Institutes of Health analysis, the national costs of cancer care is expected to increase by 40 percent, from $125 billion in 2010 to $175 billion (in 2010 dollars) in 2020.[75] The number could reach as high as $207 billion if high prices continue to be charged for new developments in oncology.[75] Currently in the U.S., the average price of a novel anticancer drug routinely exceeds US$100,000 per year[76]; a novel anti-cancer drug can now cost close to $200,000 a year or more than $16,000 a month of treatment, up $80,000 in just a few years.[77] For lung cancer specifically, the average monthly cost of these novel drugs in the U.S. is $9,945 (adjusted from the original US price in the FDA approval year to 2014), ranging from $2,069 (gefitinib, Iressa®) to $14,837 (atezolizumab Tecentriq®)[8], with prices doubling in the last decade.[6,9]

In addition, cancer regimens increasingly consist of multiple drugs (either sequential or combination therapies), which exacerbates the cost problem.[10] Combination among these different types of drugs are increasingly under evaluation (e.g., Keytruda plus chemotherapy[78], Opdivo plus Yervoy[79], durvalumab plus tremelimumab[80]). Although these novel treatments

present more options for patients, the high costs may create access and affordability challenges for patients.

2.2.2 Financial toxicity among patients with cancer

Patients undergoing cancer treatments can be burdened with high out-of-pocket costs, often described as "financial toxicity".[11–13] The resulting financial distress and even bankruptcy following cancer diagnosis[14–16] has been reported to impact patient's choice of treatment and adherence to therapy, [17–19] leading to poorer patient outcomes,[20,21] reduced quality of life,[22,23] and even greater costs of care in the long term.[20]

Lung cancer is currently one of the top five most expensive cancers nationwide and accounts for the largest proportion (13%) of cancer-related expenditures in Medicare.[48] For lung cancer patients, a 2010 report shows that the mean monthly net costs were greater than $5,000 in the initial phase of care, and among patients who died of lung cancer, mean monthly net costs were at least $7,700 in their last year of life.[75] The above estimates are likely to be understated since the study did not consider the Medicare Part D coverage under which most orally-administered anticancer and anti-nausea drugs are covered.[24] It is estimated that approximately 13% of the total Medicare expenditures for lung cancer care are paid directly out-of-pocket by patients.[48] As payers pursue cost containment strategies in response to rising drug prices, it is likely that patients will continue to experience high out-of-pocket spending.[13,81]

2.3 Drug Coverage under Medicare

Original Medicare is the traditional fee-for-service program offered directly through the federal government. It includes Part A (inpatient hospital coverage) and Part B (outpatient

medical benefit) to provide health insurance coverage for individuals aged 65 years or older. Enrollees may additionally choose to purchase a separate Part D plan (outpatient pharmacy benefit) from a private insurance provider. Under the federal Medicare program, the cost of drug treatments can be covered through either the outpatient medical benefit (Part B) or the outpatient pharmacy benefit (Part D).[24] The distinction is important because coverage varies between Medicare Part B and Part D and affects the level of expected out-of-pocket spending required for patients needing different types of anticancer drugs.

2.3.1 Medicare Part B

Medicare Part B, designed in the 1960s, is part of traditional fee-for-service Medicare (i.e., the Original Medicare) to provide outpatient medical benefits. Before implementation of Medicare's Part D prescription drug benefit in 2006, Medicare Part B was the main source of outpatient prescription drugs coverage for beneficiaries. However, drug coverage under Part B is limited within narrowly defined conditions. It generally includes injectable and infused drugs that are not usually self-administered and that are furnished and administered as part of a physician service (e.g., chemotherapies, biologics, vaccines) as well as a small number of orally-administered anticancer drugs and oral anti-emetic drugs when specific contexts apply.

Medicare Part B is administered directly through the federal government. It applies a standardized coverage structure for services included in the program; common annual deductible and coinsurance percentages for all Medicare Part B beneficiaries with standard monthly premium adjusted by income or the "hold-harmless" provision. In 2017, for example, the standard monthly premium averages $109 for 70% of beneficiaries protected under the "hold-harmless" provision, and $134 or higher depending on income for the remaining 30% of

beneficiaries. Under a standard benefit, patients with Part B also pay a deductible ($183) and/or coinsurance when receiving health services (usually 20% of the Medicare-approved cost for outpatient care).[25]

2.3.2 Medicare Part D

2.3.2.1 Overview of Medicare Part D

Before Medicare Part D went into effect, one-third of Medicare's forty-three million elderly beneficiaries had no prescription drug coverage, and, according to surveys, often restricted their medication use because of high costs.[82] Since 2006, Medicare Part D has expanded access to outpatient prescription drugs to seniors. Drugs not administered by physicians and in additional formulations, including oral and self-injectibles, are typically included.

Medicare Part D is voluntary prescription drug benefit that is offered through private insurance plans approved by the federal government. Beneficiaries can choose to enroll in either stand-alone prescription drug plans (PDPs) to supplement traditional Medicare or Medicare Advantage prescription drug plans (MA-PDs) (mainly coordinated care plans such as Health Maintenance Organizations (HMOs) and Preferred Provider Organizations (PPOs)) that integrate prescription drug coverage into all Medicare benefits under Medicare Part C. In 2017, more than 42 million of all Medicare beneficiaries (73%) were enrolled in Part D: about 6 in 10 were in PDPs and the rest in MA-PD plans.[74]

Drug coverage on Part D is determined by individual insurance companies and the designated cost-sharing requirements vary across plans. The basic benefit structure requires beneficiaries enrolling in Part D to be responsible for, in addition to monthly premiums and

annual deductible, varying cost-sharing amounts depending on the coverage phase. During the coverage gap patients pay a substantial proportion of drug costs; 100% patient responsibility before the passage of the Affordable Care Act with gradual decreases since 2011. In 2017, the Part D base beneficiary premium is $35.63, with adjustment by income. The Part D standard benefit has a $400 deductible and 25% coinsurance up to an initial coverage limit of $3,700 in total drug costs, followed by a coverage gap.[25] Although the Affordable Care Act is closing the gap over time, a patient falling into the hole still has to pay 40% of their prescription costs until the cost reaches the catastrophic coverage threshold of $8,071 in drug costs.[25] In addition, most PDPs (72%) will not offer additional gap coverage in 2017 beyond what is required under the CMS's standard benefit. Even when additional gap coverage is offered, the benefit has been typically limited to generic drugs only but not brand name drugs.[83] After entering the catastrophic coverage phase, Part D enrollees pay 5% of the price (or $3.30 for generics or $8.25 for brand-name drugs, whichever is greater) for covered drugs for the rest of the year.[25] The standard benefit amounts are indexed to change annually based on the growth rate of Part D per capita spending, and, with the exception of 2014, have increased each year since 2006.[83]

2.3.2.2 Cost management strategies

On top of the basic benefits, Part D payers may also adopt restrictive formulary structure and utilization management tools to reduce use of expensive products in the context of the steep upward trajectory of cancer-related expenditures. [28,30,31,84]

2.3.2.2.1 Formularies and drug tiering

Formularies have become a universal tool in the management of drug benefits.[31] The

scope of formulary coverage varies widely across plans as each plan may determine the drugs covered based on the CMS program guidance and the drug reference file.[85] A plan's formulary must be reviewed and granted approval under the condition that it meets the CMS's nondiscrimination requirement. That is, the plan cannot be designed in a way that substantially discourages enrollment of beneficiaries with certain health conditions. One of the key rules is a requirement that formularies must include "all or substantially all" drugs in the six protected therapeutic classes, including the anti-neoplastics class.[24]

Formulary structure consists of drug tier placement and cost-sharing amounts assigned to the tiers (through copayments or coinsurance arrangements). Typically, higher tier placement requires greater patient cost-sharing for the drug, which aims to provide financial incentives (i.e., lower cost share) to use preferred drugs over non-preferred drugs.[84,86] On average, the percentage of covered drugs facing coinsurance has greatly increased from 35% in 2014 to 58% in 2016 among PDPs.[29] Prescription drug benefits typically include at least three tiers: Tier 1 for generic drugs, Tier 2 for preferred brand-name drugs, and Tier 3 for non-preferred brand-name drugs.[84] In recent years, there has been an increase in both the number of plans using tiering and the number of tiers offered within a formulary, including use of "specialty" drug tiers[29,30,32] that often include high-priced treatments; those typically used for complex conditions including cancer.[33,34] In 2016, the vast majority of Part D enrollees (98% PDP enrollees and 96% MA-PD enrollees) enrolled in plan with five cost-sharing tiers for their formularies including a specialty drug tier (i.e., tiers for preferred and non-preferred generic drugs, preferred and non-preferred brand drugs, and specialty drugs).[30]

The growth of specialty tiering in outpatient drug formularies reflects plans' attempts to contain costs. Use of drugs placed on specialty tiers typically require patients to pay a percentage

of the drug price (i.e., coinsurance) rather than a fixed dollar amount (i.e., copayment), which often leads to patients paying more out of pocket.[35] In 2016, nearly all Part D enrollees are in plans that charge coinsurance of 25% to 33% for specialty drugs while nearly half of them (49% PDP and 43% MA-PD) are at the maximum 33% coinsurance rate.[29,30] Although cancer drugs are required to be included on Part D plan formularies due to their status as a protected drugs, coinsurance requirements assigned to the tier can result in thousands of dollars in annual out-of-pocket costs.[36] It is worth noting that while most PDPs have been applying coinsurance to high-cost drugs on the specialty tier, plans have extended coinsurance to drugs on lower tiers in recent years, including those covered on preferred and non-preferred brand tiers. [28–30] Enrollment in PDP plans with at least 2 coinsurance tiers has drastically grown from 39% in 2014 to 96% in 2016.[29] Given the high price of novel anticancer medications, patients obtaining these drugs through their Medicare Part D plans are expected to face significant out-of-pocket spending.

2.3.2.2.2 Utilization management tools

In addition to tiered cost sharing, utilization management tools may be employed to enforce formulary adherence or to manage drug costs for Part D payers more generally.[31,87] Briefly, these measures include prior authorization, quantity limits, and step therapy. According to Kaiser Family Foundation, since 2007, PDPs have applied utilization management restrictions to an increasing share of on-formulary drugs, from 18% in 2007 to 35% in 2014.[88] Drugs in higher tiers or specialty drugs are regularly subject to utilization management requirements.[36] Although these interventions are effective cost-management tools for payers, they can affect appropriate access to care and thus treatment utilization or even longer-term patient outcomes.[31,74,88]

Prior authorization

Prior authorization is an administrative tool used by a health plan or pharmacy benefit manager that requires the prescriber receive pre-approval for prescribing a drug to qualify for that drug to be covered by the plan.[89] The prescriber must justify the clinical appropriateness and medically necessity regarding the intended use of the drug. The process takes additional time for patients to obtain a covered prescription. If the request is disapproved, the prescriber could prescribe an alternate drug covered by the patient's benefit, if available, or the patient may still have the prescription filled but by paying the entire drug cost.

Prior authorization has been one major approach applied by payers to direct coverage of high-cost or newer drugs to only those patients who demonstrate a medical need for the drug or are at increased risk of developing an adverse event without the drug. Literature consistently shows that prior authorization is significantly associated with reductions in pharmacy utilization and spending.[31] There has been an increase in the share of covered drugs assigned prior authorization across PDPs, from 8% in 2007 to 21% in 2016, while application of other utilization management tools remains stable over time.[74,88] A study, which specifically analyzes differences in coverage and cost sharing for cancer drugs within Medicare Part D showed that 8-10% of cancer drugs required prior authorization in 2006.[90] However, there is limited research evaluating the longitudinal trend in prior authorization and its use for the growing number of novel and high-cost drugs approved in recent years.

Quantity limit

Quantity limits may be applied to drugs based on the approved dosage allowed over a specified period established during the FDA approval, including drugs used in cancer

treatment.[31] For example, plans may set limits on the number of pills per prescription or cap the number of prescriptions filled in a month for the covered drug. Only prescriptions within the quantity limit will be covered by the plan or the patient will be responsible for the full cost of the drugs prescribed.

Quantity limits have been used for both drug safety and cost containment. Through careful application, plans may protect their plan members from drug overuse or misuse. Meanwhile, it may help plans manage drug costs on specific medications without eliminating coverage. Over the past few years, quantity limits have been applied for more than 20% of all covered drugs among PDPs.[74] However, there is paucity of evidence evaluating the effect of quantity limits on patient care.[91,92] The limited evidence shows mixed results on patient outcomes, including reduction in the costs and utilization of disease-related services.[91,92] Moreover, quantity limits can be related to reduced use of appropriate medications[93,94] and increased long-term care admissions (e.g., nursing home[95]).[31,91,92] One study on Medicare Part D coverage and cost sharing for cancer drugs showed 3-4% of the cancer drugs covered were subject to quantity limits in the first year of Medicare.[90]

Step therapy

Step therapy protocols limit coverage to specific drugs (typically more expensive therapies) only when certain other, therapeutically-equivalent (often less expensive) drug therapies have been tried first.[31] For example, a patient is required to use generics drugs before moving to brand-name alternatives. Step therapy is often used in conjunction with prior authorization for effective pharmacy benefit management by plans.

Step therapy is one of the most popular utilization management tools in both private and public sectors, and is used 1% to 3% of covered drugs among PDPs.[74,88] Research demonstrates that step therapy can effectively encourage the utilization of first-step drugs.[31,92,96] The effect of step therapy on healthcare utilization and costs varies by clinical area. It can provide significant drug savings through the greater use of lower-cost alternatives without increasing use of other related medical services.[96] However, two studies on depression showed increases in overall and mental health-specific medical utilization and costs.[97,98] To date, only five therapy classes, including antidepressants, antihypertensives, antipsychotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and proton pump inhibitors (PPIs), have been evaluated in previous literature.[31,92,96] The adoption of step therapy has been outpacing the understanding of its clinical, humanistic, and economic outcomes.[96] A recent review finds that no published studies have specifically examined step therapy in the context of Medicare Part D and that existing evidence regarding its effect on medication quality in non-Part D plans remains inconclusive.[96] Further research on step therapy is needed for numerous therapy classes where step therapy is common and for the Medicare Part D population.

2.3.3 Cost sharing support for prescription drugs

2.3.3.1 Supplemental insurance for Medicare Part B

Despite the standard cost-sharing requirements under Part B, there are supplemental health insurance options available for beneficiaries to fully or partially pay those cost-sharing requirements, including deductibles, copayments, and coinsurance. According to the Kaiser Family Foundation, more than 80% of fee-for-service Medicare beneficiaries have some source of coverage that supplements Medicare, including Medigap, employer or union-sponsored retiree

health plans, and Medicaid for individuals with low-incomes.[26,27] First-dollar coverage Medigap plans are popular options among these options.[99,100] With first-dollar coverage, deductibles are waived and the plan provides extensive coverage for other Medicare out-of-pocket costs including 100% co-insurance and co-payments.[101] By 2015, more than 70 percent of the Medigap policyholders had plans with no cost-sharing.[99] This supplemental coverage results in more consistent and predictable spending for patients using Part B services throughout the year.

2.3.3.2 Low-Income Subsidy (LIS) for Medicare Part D

Compared to Part B, patients may face greater barriers to accessing drugs offered under Part D due to the plan's benefit structure and the lack of out-of-pocket cost protections that are typically available for drugs offered under Part B. One key exception to this lack of out-of-pocket cost protections in Medicare Part D is the Low-Income Subsidy (LIS) program.[42,43] LIS is available to Medicare beneficiaries with limited income and resources **(Table 2.1)**. [42,43] An individual is deemed eligible for a full subsidy when his/her annual income is at or below 135% of the federal poverty level (FPL) and when their resources are at or below the annually updated lower limit (e.g., $7,390 for individuals in 2017).[42,43] Beneficiaries are eligible for partial subsidies when their annual incomes are between 135-150% FPL or at or below 135% FPL with resource between the lower and higher limits (e.g., $7,390 to $12,320 for individuals in 2017).[42,43] In 2016, over 12 million (28.9% of Part D enrollees) beneficiaries are receiving drug coverage for little or no cost through LIS.[45,46]

Table 2.1 Summary of Eligibility and Cost-Sharing for Medicare Part D Benefit for Low-Income Subsidy Groups[25,42]

	LIS Eligibility Requirement	Maximum Monthly Premium	Maximum Annual Deductible	Cost- Sharing for Plan's Formulary Drugs	
				Up to Out-of-Pocket/Catastrophic Limit	Above Out-of-Pocket/Catastrophic Limit
Full LIS	• Full-benefit dual eligibles[a] • Medicare Savings Program[b] • SSI recipients[c] • Income ≤ 135% FPL with resources not exceed lower SSA limitations	$0	$0	Copay: $3.30 generics $8.25 brand	$0
Partial LIS	• Income ≤ 135% FPL with resources between lower and higher SSA limitations • Income level between 135-150% FPL	25-100%	$82	Coinsurance: 15%	Copay: $3.30 generics $8.25 brand
Non-LIS	N/A	Base at $36.56 varied by plan and adjusted by income	$400	Coinsurance: 25-51% depending on coverage phase	Coinsurance: 5% or $3.30 for generics / $8.25 for brand-name drugs, whichever is greater

Abbreviation: FPL, Federal Poverty Level; LIS, low-income subsidy; SSA, Social Security Administration; SSI, Supplemental Security Income.
Data Source: The Centers for Medicare & Medicaid Services (CMS): Full & partial LIS: 2017 Resource and Cost-Sharing Limits for Low-Income Subsidy;[42] Non-LIS: Medicare 2017 costs at a glance. 2017.[25]
[a] People eligible for both Medicare and full Medicaid benefits
[b] Supplemental Security Income (SSI) recipients, including SSI recipients who do not qualify for Medicaid, and individuals deemed to be SSI recipients.
[c] Medicare beneficiaries who are participants in the Medicare Saving Programs (MSP), which are Qualified Medicare Beneficiary Program (QMB), Specified Low-Income Medicare Beneficiary Program (SLMB), and Qualified Individual Program (QI).

The level of cost-sharing support varies between beneficiaries with full and partial subsidies **(Table 2.1)**. For a full-subsidy qualified individual, he/she is exempt from the monthly premium, annual deductible, and has no cost-sharing above the annual out-of-pocket threshold. Only a fixed copayment amounts rather than coinsurance is required for drugs that they fill before the out-of-pocket threshold (no more than $3.30 for each generic or $8.25 for each brand-name covered drug). In 2017, a partial-subsidy qualified individual receives 25% to 100% subsidy for the monthly premium, a reduction in their deductible. This group is still responsible for 15% coinsurance before reaching the out-of-pocket threshold; however, they pay no more

than $3.30 for each generic or $8.25 for each brand-name covered drug after the annual out-of-pocket threshold is met. Neither group is subject to the coverage gap where non-LIS beneficiaries are responsible for substantial proportion of the drug cost (100% before 2011) in addition to the cost sharing required for other coverage phases.

The coverage gap in Part D design has been a major concern for Medicare beneficiaries, particularly for seniors with multiple health conditions or those who need multiple medications for certain disease.[102] Research has shown that reaching the coverage gap decreases medication adherence for essential drugs, and increases drug discontinuation in many chronic illnesses, including diabetes, cardiovascular diseases, and depression, [103–108] particularly among patients taking brand-name drugs.[106,109,110] Given these effects, patients might even have higher risk of poor health outcomes in the long-term, such as hospitalizations and medical spending.[111,112] Compared to those with supplemental coverage after reaching the coverage gap, those lacking of financial assistance are more likely to experience higher out-of-pocket spending[105,113], worse adherence[105,106], as well as a doubling in discontinuing essential medications but not switching drugs[111].

Through coverage gap elimination and additional subsidies, LIS provides valuable assistance with patients' drug expenses. On average, out-of-pocket cost may account for 36-40% of total drug spending for a beneficiary without LIS and only 2-5% for those with LIS.[109] For Part D drugs specifically, the associated out-of-pocket cost of a pill could be more than a hundred times difference [44] ; the average annual out-of-pocket spending could be more than 20 times difference among high-cost enrollees.[74] In the context of anticancer therapies, this could lead to difference of thousands of dollars out-of-pocket for a single drug fill.[36,47]

2.3.4 Cost sharing support for access to cancer care

Novel cancer drugs are usually unique and under patent protection with no cheaper generic substitutes or therapeutically equivalent options available. For beneficiaries without cost-sharing subsidies, costs for initiating a novel targeted therapy on Part D can be substantial.[114] For example, a targeted therapy for advanced NSCLC, crizotinib, is priced at $14,364.38 for a 30-day supply on a Part D plan in 2017.[115] The expected out-of-pocket cost to a Medicare beneficiary filling the first single month of drug therapy would be almost $3,000.[115] However, for those with full subsidy support, the cost would be only $8.25 for the month of the treatment. With cancer regimens increasingly consisting of multiple drugs (either sequential or combination therapies), the cost problem is expected to be exacerbated in the near future.[10] This is particularly important for those in need of treatment but without appropriate resources to access the care.

It has been reported that cancer survivors are delaying or avoiding necessary care due to costs, including cost-related nonadherence[109,116–118] and treatment delays or discontinuation[119]. However, few studies consider LIS as a factor influencing treatment utilization in the cancer setting. One study on tyrosine kinase inhibitors (TKIs) among Medicare beneficiaries with chronic myeloid leukemia (CML) found that no having LIS was associated with reduced or delayed initiation of TKIs.[114] The other study on a similar population examined the factors associated with TKI initiation and adherence in CML. They found that cost-sharing subsidies, younger age, lower comorbidity, and later year of diagnosis were significantly associated with TKI initiation.[47] None of the above studies consider the difference in subsidy level by LIS status (i.e., partial vs. full subsidy).

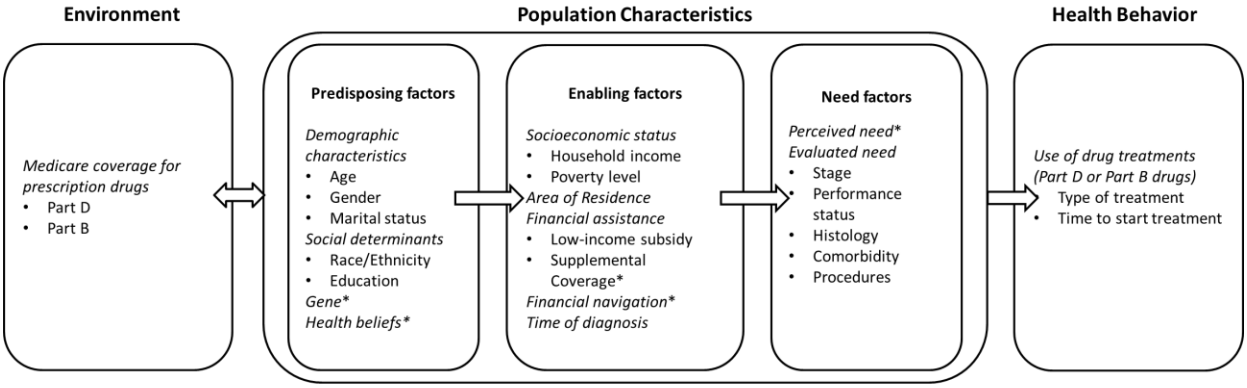
Further research is warranted for other cancers where affordability of and patient access to care are major issues in the care.[34,37–41] Lung cancer, a cancer with many novel high-cost

treatments or specialty drugs approved in the past decade for the significant unmet patient needs, is an area that needs in-depth exploration.

2.4 Conceptual Framework

The Andersen's Behavioral Model of Health Services Use forms the basis for the consideration of appropriate variables for this study.[120] The model contains three main components: external environment, population characteristics, and health behavior. Together, it posits that the use of healthcare services is a function of a set of dynamic population characteristics in the context of the healthcare environment. Specifically, these characteristics are divided in to three groups:

Figure 2.1 Conceptual Framework



1) Predisposing factors, suggesting patient predisposition to use services; these factors could be demographics (e.g., age, gender), genetic factors, and health beliefs.
2) Enabling factors, suggesting the resources that enable persons to act on their predispositions (e.g., socioeconomic status, financial assistance).

3) Need factors, representing both perceived and actual need for health care services patient need for care (e.g., cancer-related characteristics, comorbid conditions).

The proposed conceptual framework for our study, as depicted in **Figure 2.1**, is an adaptation based on the Andersen's Behavioral Model of Health Services Use.

2.4.1 Predisposing factors

Predisposing characteristics of the proposed framework include the demographic factors of age, sex, and marital status along with the social determinants of race and education level. Older age has been consistently shown to be associated with lower use of treatment in the advanced NSCLC setting.[121–125] Female patients are found to be more likely to receive biomarker testing as well as timely and appropriate treatment.[121,126–129] Although women appear to have higher risk of adverse effect from treatments[130–133], they tend to have improved survival compared with men.[126,134–137] Marital status suggests the presence of social support for a patient.[138,139] A recent meta-analysis suggests that, among a cancer population, marital status would have effects on health behaviors (e.g., treatment-seeking, treatment compliance), access to the health care systems and assistance with navigating its complexities, the likelihood of receiving vigorous and aggressive, active cancer treatment.[139] All of these could have either direct or indirect effect on treatment uptake and survival. These observations have also been supported by several studies in lung cancer populations in the literature; married patients are more likely to receive treatment, including surgery, radiation, and systemic therapy, and have better prognosis than unmarried patients.[121,140–144]

A growing base of evidence has demonstrated disparities by race/ethnicity with respect to receipt of appropriate care in NSCLC population.[121,127,145–156] Minority groups experienced

inequalities throughout all areas of the cancer spectrum, spanning screening, diagnosis, and treatment, as well as survivorship and end-of-life care. Another social determinant, education level, has also been associated in patients with lung cancer with greater care intensity (e.g., diagnostic procedures and multidisciplinary care) and longer survival experienced among patients with high education as compared to low education.[157–160] Because socioeconomic data are not collected at the individual level within the SEER-Medicare database, we measure education at the census tract level to serve as a proxy measure of education at the individual level.

Genetic susceptibility could potentially influence need and response to treatment for NSCLC.[51,161] However, information on genetic mutations and test results are not regularly collected in population-level registry-linked claim databases to date. In addition, health beliefs, consisting of patient personal attitudes, values, and knowledge related to health and health services, may affect the perception of whether they need health services or not but this information cannot be obtained within the SEER-Medicare databases.

2.4.2 Enabling factors

Enabling characteristics of the proposed framework include socioeconomic status (e.g., income), area of residence at diagnosis (e.g., state/region, urban residence), financial assistance (e.g., low-income subsidy, supplemental insurance options), financial navigation, and time at diagnosis (e.g., year of diagnosis, diagnosed month). Disparity by socioeconomic status, including income and poverty level, in cancer outcomes has been well documented, suggesting that potential association between lower socioeconomic status and poorer access to treatment as well as greater risk of mortality.[121,159,160,162] Given that the SEER-Medicare program does not

collect individual measures of socioeconomic status for patients, census tract level median household income and poverty information are used as proxy measures for individual level data. Area of residence may play a role in treatment access as local policy could be influential to availability of financial assistance, insurance plan design, as well as pharmaceutical prescribing or treatment modality across geographic regions.[83,163–166] Furthermore, individuals residing in rural areas may be more likely to live in poorer areas with a limited supply of health care providers. [163,164]

Low-income subsidy and supplemental insurance are resource to alleviate patient out-of-pocket burden for prescription drugs and thus improve affordability of care. Without the financial assistance, significant out-of-pocket costs would be incurred following a diagnosis of cancer.[40,167,168] High out-of-pocket cost have been shown association with suboptimal utilization of essential treatments in cancer care, including decreasing adherence[17,34,169], persistence/discontinuation[17,34,119], delay initiation[34,114,119,170], and treatment abandonment[34,170]. High out-of-pocket costs for patients who do not receive a low-income subsidy could be related to treatment delay and discontinuation.[114,119] These observations are especially true for expensive orally-administered cancer drugs covered under Medicare Part D.

Although Part B supplemental insurance information is not directly measured in Medicare data, we expected there to be a limited effect of supplemental Part B coverage at the population level as most of fee-for-service Medicare beneficiaries have some source of supplemental coverage.[171]

Financial navigation is a financial counseling program that educates patients about their financial responsibility, optimizes patient coverage, and maximizes external cost-sharing assistance in oncology setting.[172,173] The ultimate goals of financial navigation are to address

access barriers to health services, decrease the financial burden of cancer care and thus to reduce delays in delivering timely care and poor health outcomes for cancer patients.[172,173] However, the service is usually provided for patients receiving care at hospitals or cancer centers. While financial navigation cannot be directly measured in the Medicare data, we can explore the use of proxies for access to financial navigation services by including a measure of whether a patient was treated at an NCI-designated comprehensive cancer center.

Finally, time of diagnosis is expected to affect treatment utilization in two ways. First, year of diagnosis is associated with greater variety and availability of treatments for patients as more treatments are approved and diffuse into clinical practice over time.[174–176] Second, patients needing an expensive therapy may decide to delay treatment initiation if diagnosed late in the benefit year to avoid facing very high out-of-pocket costs in back-to-back fills when the benefit year resets.[1099,40]

2.4.3 Need factors

Need factors of the proposed framework include perceived needs and evaluated needs (e.g., tumor stage, comorbidity). Perceived need for health care services is how people view and experience their own general health, functional state and illness/symptoms. Patient perceptions about the importance and magnitude of a health problem would lead to a decision to seek medical care or not. In other words, people tend to take action to manage illness if they (a) believe that they are susceptible to that illness, especially if they view the illness as potentially having serious consequences to them; (b) believe that by following a recommended health action (e.g., treatment initiation), they would reduce their susceptibility to or the severity of the illness; (c) believe that the benefits of taking the recommended action outweigh the perceived barriers or

costs for doing; (d) are aware of the illness and have information or resource regarding the approaches to manage the illness; and (e) are confident of their ability to manage the illness.[177] Overall, perceived need can be determined health beliefs.[178–183] The information on perceived need is not available in the SEER-Medicare databases.

Nevertheless, we are able to estimate evaluated need. Evaluated need represents professional assessments and objective measurements of patients' health status and need for medical care. This more measurable and unprejudiced need include in our proposed framework include tumor status (e.g., stage, grade, histology), other comorbid conditions, and medical procedures performed besides pharmaceutical treatments (e.g., receipt of radiation). Patient tumor and comorbid characteristics may significantly influence the need for and expected benefit from treatment.[51,184,185] As a result, they would affect the treatment modalities recommended and received as well as the timing of treatment uptake among patients with NSCLC.

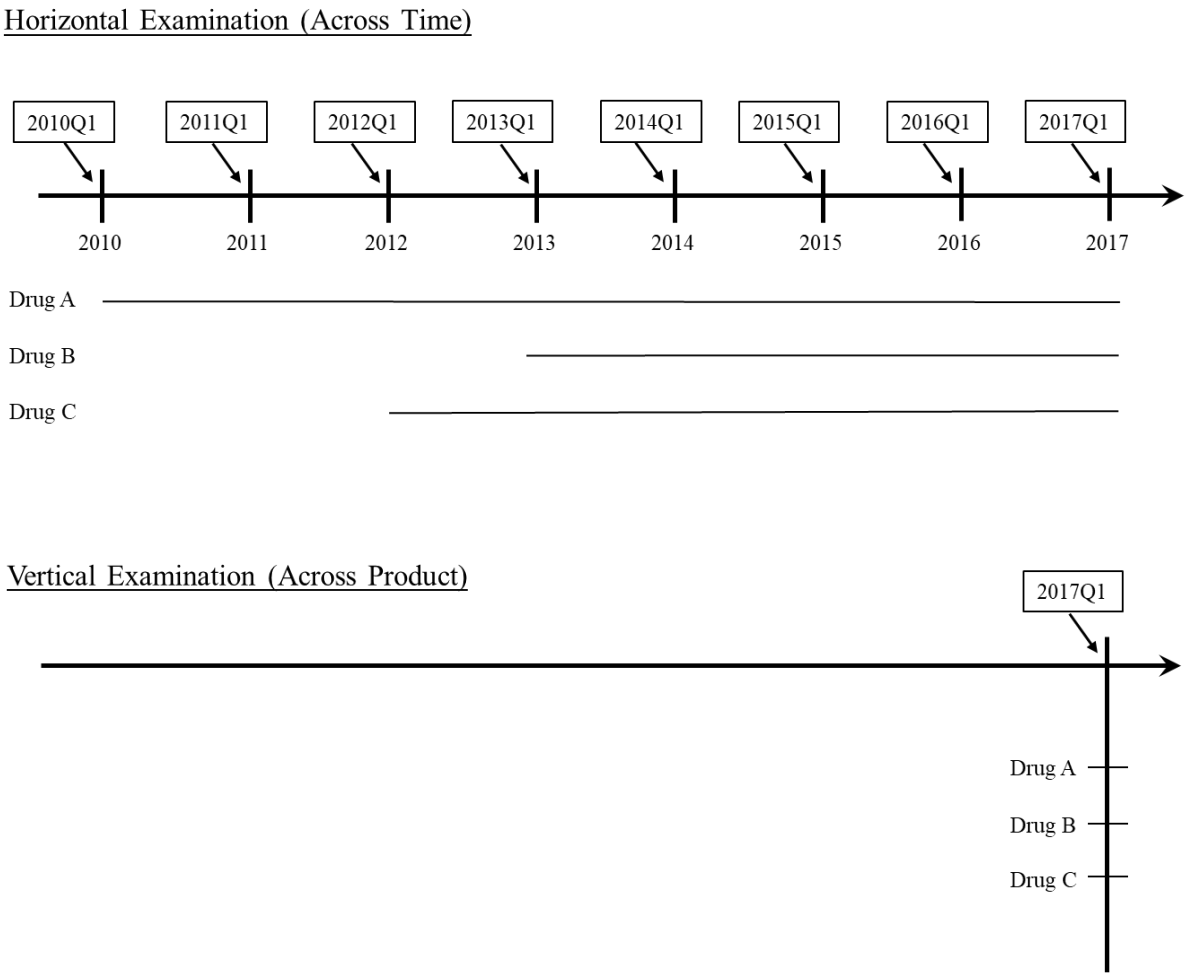
CHAPTER THREE: RESEARCH METHODS

3.1 AIM 1 – Examine changes in drug-specific price, formulary structure, and the use of utilization management tools for Part D medications approved for advanced NSCLC from 2009 to 2017.

3.1.1 Data Source

The Prescription Drug Plan Formulary, Pharmacy Network, and Pricing Information Files from the Centers for Medicare & Medicaid Services (CMS) contain formulary, pharmacy network, and pricing data for Stand-alone Medicare Prescription Drug Plans (PDPs) and Medicare Advantage Prescription Drug Plans (MA-PDs). These public use files are comprised of non-identifiable data tables, including Plan Information, Geographic Locator, Formulary, Beneficiary Cost, Pharmacy Network, and Drug Pricing. The Plan Information file contains contract ID, plan ID, and segment ID, which together allow data linkage across tables to retrieve detailed plan-level (or formulary-level) data, including plan service area, plan type, plan benefit design, plan pharmacy networks, National Drug Codes (NDCs), cost share tier level, indicators for utilization management, and cost-sharing arrangement for drugs. The data are available in quarterly files, which are first available in quarter 1, 2009. Therefore, we are able to use the dataset to identify coverage for a specific drug on each of the available plans/formularies as well as changes in coverage over time.

Figure 3.1 Study Design for Aim 1



For this aim, we used the first quarter of data for each year from 2010 to 2017 to evaluate the change in drug price and coverage for Part D advanced NSCLC drugs during 2010 to 2017 (number of years studied for each drug depended on its year of FDA approval); the most updated quarter data available (Q12017 as of 06/2017) was also used for an overall evaluation across all advanced NSCLC drugs available by that time. **Figure 3.1** summarizes the design for both the horizontal comparison (same product across time) and vertical comparison (same time point across products). We used plan/formulary as the unit of analysis to understand the coverage provided for each advanced NSCLC drug across all Medicare Part D plans in the United States.

To provide a more comprehensive assessment of drug affordability, we also presented information on Part B drug pricing for products available in 2017 using the Average Sales Price (ASP) data provided by CMS.

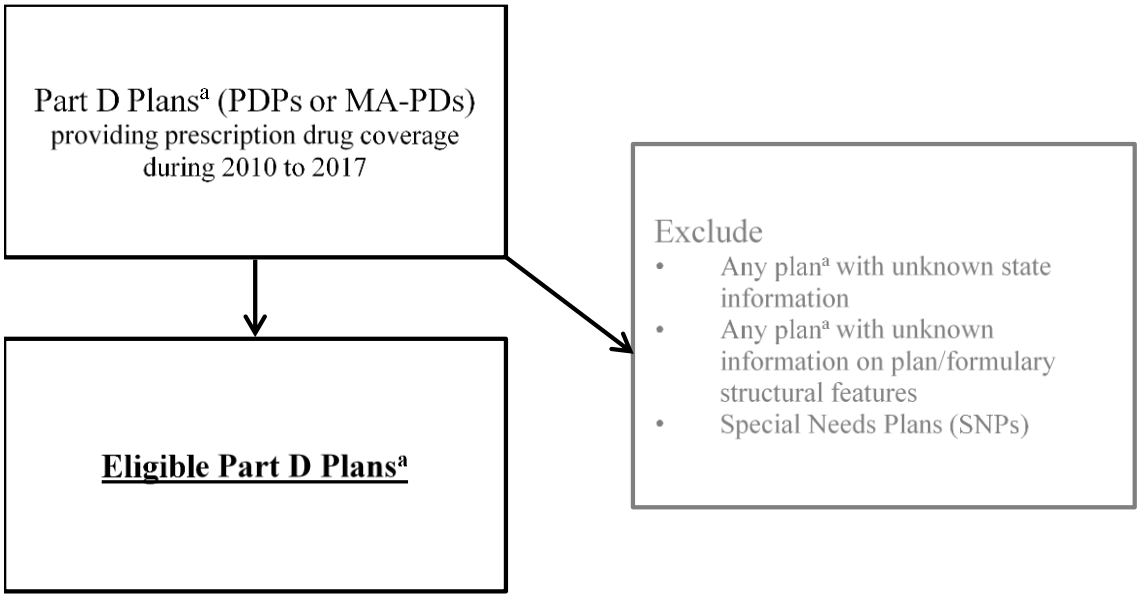
3.1.2 Study Design

3.1.2.1 Sample selection

The sample consisted of health plans which provide prescription drug coverage, including Stand-alone Medicare Part D prescription drug plans (PDPs) and Medicare Advantage Prescription Drug Plan (MA-PDs) during 2010 to 2017; plans available during the first quarter of each year from 2010 to 2017 for across time examination and during the first quarter of 2017 (most updated data as of June 2017) for a most up-to-date comparison across product. Each plan/formulary serves as the unit of analysis for the examination. Please note that if a plan sponsor (e.g., United Healthcare) provides a national plan and a state plan, it would be counted as two plan/formularies.

We identified Part D plan/formularies' coverage design and formulary structure for Part D anti-cancer medications with FDA approved indications for treating advanced NSCLC as of June 2017 **(Table 3.1)**. Plans were excluded if the information on state or plan/formulary structural features is unknown. We also excluded Special Needs Plans, which accounted for 10% of the Part D plans, since they target subgroups of beneficiaries (e.g., institutionalized individuals) and may have specialized formularies.[186,187] **Figure 3.2** summarizes the inclusion and exclusion criteria for the cohort of Aim 1.

Figure 3.2 Flow Diagram of Study Plan Selection for Aim 1



[a] if a plan sponsor (e.g., United Healthcare) provides a national plan and a state plan, it would be counted as two plan/formularies.

3.1.2.2 Drugs of Interest

Table 3.1 Advanced Non-Small Cell Lung Cancer Drugs covered under Part D and approved by U.S. FDA by June 2017[a]

Aim			Drug Name	Brand Name	Year of Initial Approval for advanced NSCLC	Therapeutic Class
Aim 1	Aim 2	Aim 3	Gefitinib	Iressa	2003	Targeted therapy – EGFR Tyrosine kinase inhibitor
			Erlotinib	Tarceva	2004	Targeted therapy – EGFR Tyrosine kinase inhibitor
			Crizotinib	Xalkori	2011	Targeted therapy – ALK Tyrosine kinase inhibitor
			Afatinib	Gilotrif	2013	Targeted therapy - EGFR Tyrosine kinase inhibitor
			Ceritinib	Zykadia	2014	Targeted therapy – ALK Tyrosine kinase inhibitor
			Alectinib	Alecensa	2015	Targeted therapy – ALK Tyrosine kinase inhibitor
			osimertinib	Tagrisso	2015	Targeted therapy – EGFR T790M Tyrosine kinase inhibitor

[a] See **Appendix Table 3.1** for more detailed drug information of the Part D drugs of interest; see **Appendix Table 3.3** for the NDC codes used for identifying each drug of interest.
Abbreviation: ALK: Anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; mTOR: mammalian target of rapamycin; T790M: threonine at amino acid position 790; TKI: tyrosine kinase inhibitor.

Table 3.2 Advanced Non-Small Cell Lung Cancer Drugs covered under Part B and approved by U.S. FDA by June 2017[a]

Aim			Drug Name	Brand Name	Year of Initial Approval for advanced NSCLC	Therapeutic Class
Aim 1	Aim 2	Aim 3				
			Cisplatin	Platinol	1994[b]	Traditional Chemo – Platinum-based agent
			Etoposide (VP-16)	Vepesid Etopophos	N/A[c] N/A[d]	Traditional Chemo – DNA topoisomerase inhibitor
			Carboplatin	Paraplatin	1999[c]	Traditional Chemo – Platinum-based agent
			Paclitaxel	Taxol Abraxane	1998 2012	Traditional Chemo – Taxane
			Vinorelbine	Navelbine	1994	Traditional Chemo – Vinca alkaloid and analog
			Docetaxel	Taxotere	1999	Traditional Chemo – Taxane
			Gemcitabine	Gemzar	1996	Traditional Chemo – Pyrimidine analog
			Pemetrexed	Alimta	2008	Traditional Chemo – Folate analog metabolic inhibitor (i.e., antifolate)
			Bevacizumab	Avastin	2006	Targeted therapy – Monoclonal antibody on VEGF
			Ramucirumab	Cyramza	2014	Targeted therapy – Monoclonal antibody on VEGF
			Nivolumab	Opdivo	2015	Targeted therapy/immunotherapy – PD-1 Inhibitor
			Pembrolizumab	Keytruda	2015	Targeted therapy/immunotherapy – PD-1 Inhibitor
			Necitumumab	Portrazza	2015	Targeted therapy– monoclonal antibody on EGFR

[a] See **Appendix Table 3.2** for more detailed drug information of the Part B drugs of interest; see **Appendix Table 3.4** for the HCPCS codes used for identifying each drug of interest.
[b] Indication for NSCLC is not specified in the cisplatin's labeling. However, within the approval of vinorelbine in 1994, cisplatin was used as combination treatment for advanced NSCLC.
[c] Indication for NSCLC is not specified in the etoposide's labeling. However, etoposide has long been recommended in combination use with platinum-based agent by the NCCN Guidelines.
[d] Indication for NSCLC is not specified in the carboplatin's labeling. However, within the approval of decetaxel in 1999, carboplatin was used as combination treatment for advanced NSCLC.
Abbreviation: EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; VEGF: Vascular endothelial growth factor.

Drugs of interests were Part D anti-cancer medications with FDA approved indications for treating advanced NSCLC as of June 2017 **(Table 3.1)**. Drugs were excluded from the analysis if the drug was not yet available (e.g., brigatinib) at the time of data release.

Advanced NSCLC drugs covered under Part B were additionally considered in the examination of prices **(Table 3.2)** in order to complement the overview regarding the pricing of all drug treatments available for advanced NSCLC, despite of coverage source, in the recent decade.

Please note that for all the analysis in this aim, since we used data from the first quarter of each year, drugs approved later in the calendar year would be included in estimates from the next calendar year.

3.1.2.3 Outcome Measurement

Drug Price

Drug prices for Part D drugs were retrieved from the Pricing file; representing the plan level average cost of a drug for specified days supply at in-area retail pharmacies. The price for a 30-day supply of the most commonly covered dose of each drug was identified. Median costs were then calculated among plans with corresponding ranges (minimum and maximum) reported.

In the examination of drug prices, we additionally presented the prices of advanced NSCLC drugs covered under Part B **(Table 3.2)**. This additional examination aimed to complement the overview regarding the pricing of all drug treatments available, despite of coverage source, over the past decade. For that, we excluded Part B drugs that were removed from the NCCN Clinical Practice Guidelines™ Non-Small Cell Lung Cancer 9th version 2017 (e.g., vinblastine, mitomycin, ifosfamide) for its rare use in clinical practice or those with no recommended regimen specified in the Guideline (e.g., irinotecan). Drugs that had no specific J code effective (e.g., atezolizumab) at the time of data release were also not considered for this examination.

Drug prices for Part B drugs available in 2017 (approved as of June 2017, **Table 3.2**) were obtained from the average sales price (ASP) data provided by CMS. Estimation of monthly price was based on previously published methodology.[9] Because infused drugs are often billed

per unit based on patient size, we calculated the price for a 12-week dosing regimen for an average adult who weighs 70 kg or has a body-surface area of 1.7 m^2. This value was then divided by 2.77 (to obtain a 1-month price) and further multiplied by 106% (to reflect the standard reimbursement from Medicare Part B for physician-administered drugs of ASP+6%).[9] This estimated price would reflect the total price of the Part B drug in 2017, including the amount from Medicare reimbursement and the amount paid by the patient or by a third-party payer. The lowest total dosing regimen[9] for advanced NSCLC recommended by the NCCN Guideline was used for the calculation for each drug. Median monthly prices were reported for individual drugs.

We measured overall changes in price paid by Medicare for each product covered during 2010 to 2017. For the longitudinal evaluations, prices were inflated to 2017 based on the Consumer Price Index (CPI)[188] for prescription drugs.

Coverage Design and Formulary Structure

Medicare Part D formulary structures provide a view of how individual drugs are covered under each available health plan, utilization management tools in place to restrict treatment access, and the extent of cost sharing required by patients needing the drug of interest. We evaluated three structural plan/formulary features applied to each included Part D drug product by each Medicare Part D plan available during the study period: formulary drug tier, patient cost-sharing arrangement (i.e., use of copayments versus co-insurance), and the application of utilization management tools (including prior authorization (i.e., the plan must grant permission before a particular drug can be prescribed and qualified for coverage), quantity limit (i.e., restriction on the amount of drugs a plan will cover over a certain period of time), and step

therapy (i.e., use less expensive drug options before “stepping up” to treatments that cost more)).. To understand how benefits coverage has changed over time, we measured overall changes in the benefit design and formulary structure for each product covered during 2010 to 2017. Two types of prescription drug plans, PDPs and MA-PDs, were treated separately. For drugs approved on or before 12/31/2009 we assessed changes for each year from 2010 to 2017; for drugs approved after 12/31/2009 we assessed changes from the year of FDA approval to 2017. An evaluation encompassing all available drugs was performed in the most recent quarter-year (i.e., Q12017).

We first reported the proportion of plan/formularies covering individual drugs of interest in each year as well as the proportion of plan/formularies covering at least one medication from each therapeutic class in each year.

For understanding formulary tier placement for each Part D anticancer drug available in each year, we used the Beneficiary Cost File to identify the product’s tier placement in each Medicare Part D formulary, the total number of tiers designed in the associated plan, and whether the designated tier of the drug is a specialty tier. We calculated the percentage of plan/formularies placing the drug on the top tier and the percentage of plans placing the drug on the specialty tier.

Next, cost-sharing arrangements were defined based on three features of the benefit design, including the type of cost sharing designated for the tier, the associated coverage phase, and type of dispensing pharmacy. The three components were provided by the Beneficiary Cost File. There were two types of cost-sharing approaches: copayment or coinsurance; three coverage phases: initial coverage, coverage gap, and catastrophic phases; three types of pharmacies: preferred, non-preferred, and mail order. For this study, we focused on cost-sharing requirement for preferred pharmacy. That is, the type of cost sharing designated for the tier of the

drug at preferred pharmacies during the associated coverage phases. We reported the proportion of plans applying copayments (a flat fee per fill) versus coinsurance (a percentage of the drug price) as well as the median cost-sharing amount (absolute dollars if copay was used; percentage if co-insurance was used).

Application of utilization management tools was determined by whether the drug was subject to quantity limit, prior authorization, and step therapy. Information is available in the Basic Drugs Formulary File, Excluded Drugs Formulary File, or Beneficiary Cost File. We measured the percentage of plan/formularies requiring each of the three tools for a specific drug.

All the abovementioned measurements for plan/formulary features were reported in a drug-specific and annual fashion.

Expected Patient Out-of-Pocket Cost

To understand the actual financial burden on patient for starting a Part D treatment, particularly those without subsidy support,we also identified corresponding amounts of patient cost-sharing for the initial month of drug use during a calendar year for a non-LIS patient enrolled in a standard Part D plan in 2017 for . We calculated the median out-of-pocket costs for a 30-day supply with the assumption that the patient did not have any other Part D costs prior to this initial fill of advanced NSCLC treatment.

3.1.2.4 Analysis

Descriptive statistics were used to characterize the changes in drug price, formulary structure, and benefit design. All analyses will be performed in SAS 9.3 (SAS Institute, Cary NC)

Table 3.3 Summary of Unit of Analysis, Covariates, and Outcomes for Aim 1

	Type	Definition	Source File
Unit of analysis			
Plan/formulary	Unique ID	A unique ID assigned to each plan/formulary	Formulary Files
Time			
Year	Categorical	2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014	Basic Drugs Formulary File
Outcomes			
Median advanced NSCLC drug price	Continuous	Median price with interquartile range for a 30-day supply of the most commonly covered dose of each advanced NSCLC drug (in 2017 dollar).	Pricing File, ASP File
Top tier placement	Binary	Whether the formulary tier associated with the advanced NSCLC drug is the top tier within the plan (Yes; No)	Beneficiary Cost File
Application of specialty tier	Binary	Whether the designated tier of the advanced NSCLC drug is a specialty tier (Yes; No)	Beneficiary Cost File
Cost-sharing arrangement	Categorical	Use of copayment or co-insurance at different coverage phase for the advanced NSCLC drug	Beneficiary Cost File
Application of utilization management tools	Binary	1) Whether the drug was subject to quantity limit (Yes; No) 2) Whether the drug was subject to prior authorization (Yes; No) 3) Whether the drug was subject to step therapy (Yes; No)	Basic Drugs Formulary File, Excluded Drugs Formulary File, Beneficiary Cost File.
Median drug cost in the initial month of use	Continuous	Median patient OOP on an advanced NSCLC drug cost in the first month of use within a calendar year	Beneficiary Cost File, Pricing file

Abbreviation: NSCLC, non-small cell lung cancer; OOP, out-of-pocket cost.

3.2 AIM 2 – Examine trends in the utilization of advanced NSCLC medications by coverage source (i.e., Medicare Part B or Part D). In addition, to identify clinical, sociodemographic, and health system factors associated with the use of Part D treatments among patients diagnosed with advanced NSCLC from 2007 to 2014.

3.2.1 Data Source

The SEER–Medicare database represents a linkage of two population-based data sources – the SEER cancer registry and fee-for-service Medicare claims data – that provides detailed health information about Medicare beneficiaries with cancer. Since 1973, the SEER program of the National Cancer Institute has been collecting data from 18 population-based cancer registries of all incident cancer cases in diverse geographic areas, which covers approximately 30 % of the US population. It is a primary source of nationally representative data on cancer incidence and survival in the U.S., and contains information on patient demographics, tumor characteristics, and first course of treatment.

Medicare is the federal funded health insurance program for older people aged 65 or older, individuals with disabilities, as well as those with end-stage renal disease. In particular, it is the primary insurer for 97% of the older population in the U.S. Medicare program and provides 4 parts of coverage for specific services: Part A for inpatient hospital services; Part B for supplemental medical services provided mostly on outpatient basis (Part A and Part B together are known as the traditional fee-for-service Medicare); Part C (also known as Medicare Advantage), a managed care options for additional services excluded from Parts A and B; Part D, implemented since 2006, for prescription drug benefit. According to Kaiser Family Foundation, around 70% of the Medicare enrollees were in traditional fee-for-service Medicare and the rest in Medicare Advantage. For the project, we focused on traditional fee-for-service Medicare as the

claims databases provide comprehensive longitudinal information on inpatient, outpatient as well as pharmacy services used by individuals enrolled in fee-for-service Medicare Parts A, B and D.

The SEER-Medicare linked databases includes the Patient Entitlement and Diagnosis Summary File (PEDSF), which contains basic patient demographics, cancer-related characteristics, Medicare entitlement and enrollment, and health service utilization. In addition, census tract and zip code-level census data including socioeconomic information from the 1990 and 2000 Censuses and the 2008 – 2012 American Community Survey are included.

The fee-for-service Medicare files includes Part A inpatient service (MEDPAR, Medicare Provider Analysis and Review), Part B institutional outpatient services (Outpatient Claims), Part B non-institutional outpatient services (NCH, National Claims History), home health services (HHA, Home Health Agency), hospice care, and durable medical equipment services (DME, Durable Medical Equipment). Prescription drug coverage and utilization through Medicare Part D is also available (PDE, Prescription Drug Event file) since 2007.

The population-based linked database serves as the foundation for epidemiological and health services research in cancer populations. Currently, the linkage is updated biennially through the concerted efforts among the National Cancer Institute, the SEER registries, and the Centers for Medicare and Medicaid Services (CMS). As of the most recent update in 2016, the data include all Medicare eligible persons appearing in the SEER data who were diagnosed with cancer through December 31, 2013, and their Medicare claims through December 31, 2014.

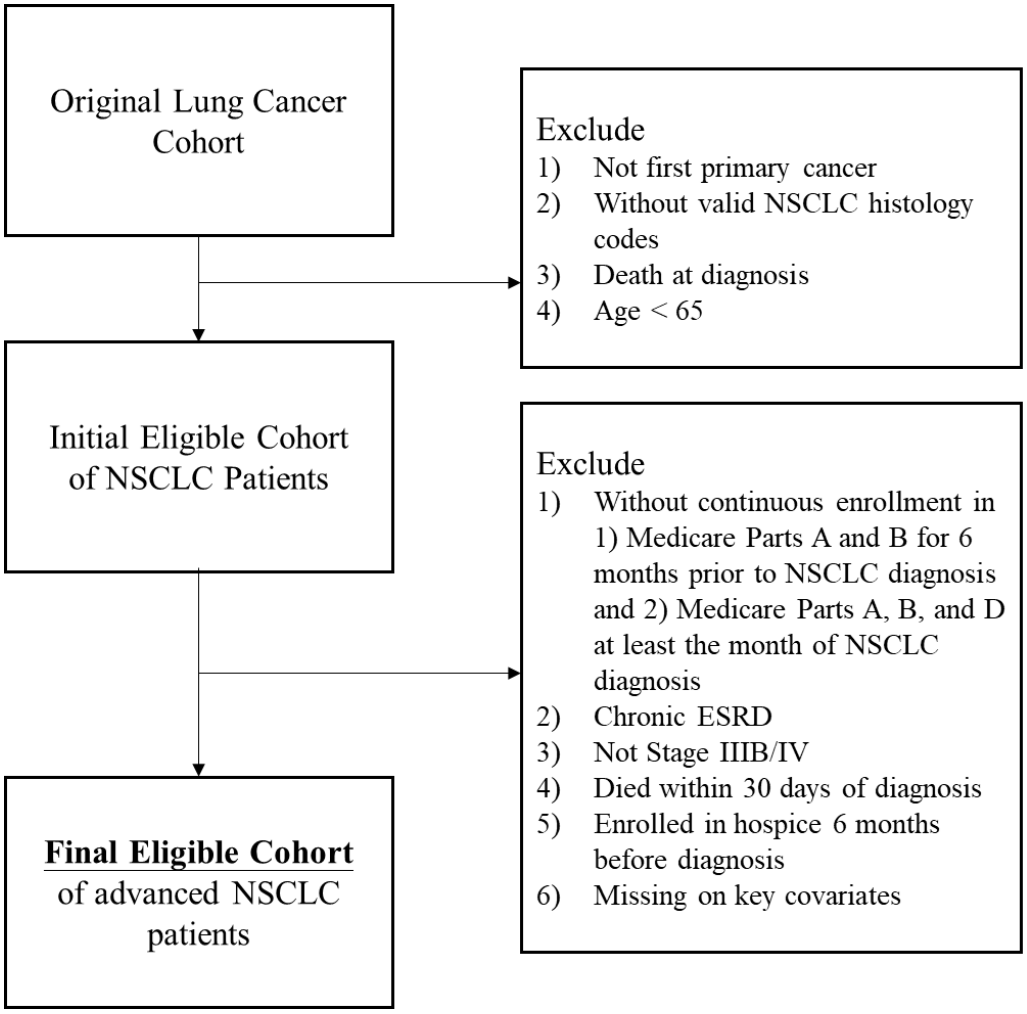
3.2.2 Study Design

3.2.2.1 Cohort Selection

The study population consisted of a retrospective cohort of patients aged 65 or older and

diagnosed with locally advanced or metastatic non-small cell lung cancer (NSCLC), stages IIIB/IV (based on American Joint Committee on Cancer Stage Group (AJCC), 6th edition staging) between July 1, 2007, and December 31, 2013. We refined the cohort to include only patients with NSCLC as their first or only primary cancer during the study period. We excluded patients whose Medicare eligibility was based on end-stage renal disease (ESRD) or disability as these patients likely have different health-care related needs than patients qualifying for Medicare due to age. To minimize misclassification of outcomes, we required patients to have continuous enrollment in 1) Medicare Parts A and B for 6 months prior to NSCLC diagnosis and 2) Medicare Parts A, B, and D from the month of NSCLC diagnosis through death, disenrollment, 12 months since diagnosis, or the end of data (December 31, 2014), whichever occurred first. Patients enrolled in Medicare Advantage plan (health maintenance organization) for the same period were excluded since their claims are not available in the SEER-Medicare database. In addition, we excluded patients who had missing information regarding diagnosis or inconsistent death records between SEER and Medicare, whose diagnosis were made by death certificate or autopsy, or who died within 30 days after diagnosis. We further excluded patients enrolled in hospice before or at the time of diagnosis because patients in hospice care are certified by their doctor as being terminally ill and would no longer receive curative treatment for their underlying disease. Detailed selection criteria for the cohort are summarized in **Figure 3.3.**

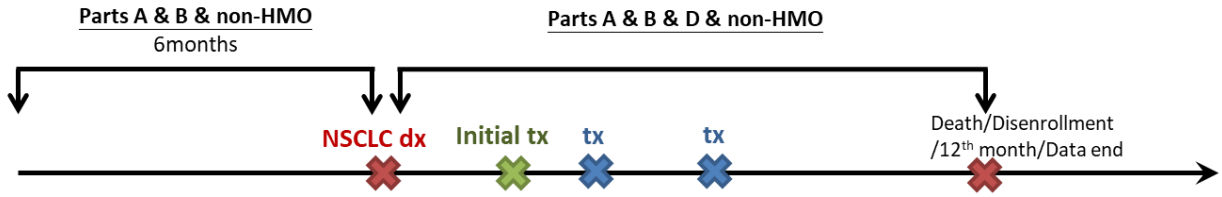
Figure 3.3 Flow Diagram of Study Population Selection for Aim 2



Abbreviation: NSCLC, non-small cell lung cancer; ESRD, end-stage renal disease

The study design includes a six-month period prior to the diagnosis of NSCLC to measure the baseline patient characteristics (see **3.2.2.3** for the covariates considered**)**. We followed patient from the diagnosis until death, disenrollment, the 12th month since diagnosis, or the end of data (December 31, 2014), whichever occurred first. This post-diagnosis period was used to identify the outcomes of interest (see **3.2.2.2)**. The study design of this aim is shown in **Figure 3.4.**

Figure 3.4 Study Design for Aim 2



3.2.2.2 Outcome Measurement

Utilization of anticancer therapies reflects both the clinical practice of oncology as well as patient access to care. In this aim we examined changes in both Part D and Part B covered anticancer medication use over time for patients with NCSLC. Drugs of interest included those with United States FDA approvals for advanced NSCLC by the end of 2014 **(Table 3.1 and Table 3.2)**. The primary outcome of interest was whether a patient ever filled an anti-cancer drug on Medicare Part D from diagnosis through the end of follow-up, up to one-year post diagnosis. The use of studied drugs was identified between 2007 and 2014 while the annual utilization rates were presented based on patients' year of advanced diagnosis (i.e., 2007-2013). The rate was calculated as the number of advanced NSCLC patients on a specific drug divided by total number of advanced NSCLC patients during a year. In addition to examination of each specific drug, we also assess the overall utilization of Part B and Part D drugs, respectively.

In addition, we explored the effect of clinical, sociodemographic, and health system factors on the use of Part D drugs among patients diagnosed with advanced NSCLC from 2007 to 2014. The use studied was "ever use a Part D anti-cancer drug within 12 months since the diagnosis of NSCLC." That is, a patient would be counted a Part D drug user if he/she had ever used a Part D anti-cancer drug for advanced NSCLC from diagnosis through end of follow-up. Detailed information on the covariates included please see **section 3.2.2.3**. **Table 3.4**

summarized the outcome for Aim 2.

Table 3.4 Summary of Outcomes for Aim 2

Variable	Type	Definition	Source File
Outcomes			
Annual rates of people on specific drug(s)	Dichotomous	Number of advanced NSCLC patients on a specific drug divided by total number of advanced NSCLC patients during a year.	PDE
Ever use a Part D anti-cancer drug within 12 months of diagnosis	Dichotomous	A patient was counted as an ever user of Part D drug if he/she had ever used a Part D anti-cancer drug for advanced NSCLC from the diagnosis through end of follow-up.	PDE

Abbreviation: PDD, Prescription Drug Event file.

3.2.2.3 Covariates

The six-month period prior to the diagnosis of NSCLC **(Figure 3.3)** was used to measure the baseline characteristics of the study population (**Table 3.5)**, including:

- Demographic characteristics
  - Age: Age was calculated as difference between the month and year of birth and the month and year of diagnosis in the PEDSF file. It was further measured in both continuous and categorical approaches. For continuous measurement, we calculated mean and standard deviation. For categorical measurement, we classified patients into 3 age groups: 65-69, 70-74, 75-79, 80 and older.
  - Sex: Sex is a categorical variable based on the information provided in the PEDSF file; 1 as ‘male’ and 2 as ‘female’.
  - Race/ethnicity: Race and Hispanic ethnicity information was combined using the SEER variable and was further categorized into Non-Hispanic White, Non-Hispanic Black, Hispanic, and Others based on the established algorithm.

- Marital status: Marital status at diagnosis was divided into following groups: Single (including those in separated, divorced, widowed, or unmarried status, and those having domestic partner (same sex or opposite sex or unregistered)), Married (including common law), Unknown.

❖ Institution affiliation***: Institution affiliation was provided in the SEER-Medicare Provider file, including affiliation with the Eastern Cooperative Oncology Group (ECOG), NCI cancer center designation, teaching hospital designation, and level of affiliation with a medical school. The provider file can be linked to MEDPAR and Outpatient files. Therefore, we used the linkage to identify patients receiving care (i.e., any chemotherapy/radiation) for their advanced NSCLC in the aforementioned institutions during follow-up period defined above. Indicator variables were created for each type of institution affiliation for every patient.

❖ Geographic characteristic

- SEER registry region: SEER registries were grouped into 5 regions based on the state and region where a patient was diagnosed in PEDSF. There are Northeast (Connecticut, New Jersey), South (Kentucky, Louisiana, Atlanta, Rural Georgia, Greater Georgia), North Central (Iowa, Detroit), West (Hawaii, New Mexico, Utah, San Francisco, San Jose, Los Angeles, Greater California, Seattle), and Other/Unknown.
- Urban residence: The coding definition provided in PEDSF, Rural/Urban Continuum Codes, is based on the classification scheme developed by Economic Research Service of the Department of Agriculture. The classification considers population size, degree of urbanization, and adjacency to a metro area. We applied this definition to classify patients into 6 groups: Big metro (Counties of metropolitan areas of 1 million

population or more), Metro (counties in metropolitan areas of less than 1 million population), Urban (non-metropolitan counties with urban population of 20,000 or more), Less Urban (non-metropolitan counties with urban population of 2,500-19,999), Rural (non-metropolitan counties which are completely rural or with less than 2,500 urban population), and Unknown.

- Socioeconomic characteristics: In SEER-Medicare linked data, there is no individual-level information available for socioeconomic variables such as household income and education. Thus, the related information used in the analysis will be based on aggregate measures from the US Census Bureau as a basis for inference about individuals. The information can be obtained from the Census Tract and Zip Code files. For this study, census tract-based data is preferred over the zip code-based ones. This is because the former covers relatively homogeneous units with respect to population characteristics, provides richer and more reliable geographically-based socioeconomic data, and provides static geography information from census to census. Data collected from the American Community Survey (ACS) in the Census Tract file was used to create census-tract-based socioeconomic characteristics for the study population.
  - Education: Education attainment at the census tract level in the Census Tract File was measured as the percentage of persons aged 25 and older with less than high school degree within the same census tract as the patient. We used this variable and further divide our population into four groups: <5%, 5%–<10%, 10%–<20%, and ≥20% of the residents without high school degrees.
  - Income: Median household income measured at the census tract level in the Census Tract File was used to represent the median income for all individuals in the same

census tract as the patient. We further divided the study population into four groups based on the quartile values of this income variable.

- Census Tract Poverty Indicator: According to census-tract poverty level, the percentage of residents in a census-tract below the official poverty threshold, census-tract poverty was grouped into four categories: <5%, 5%–<10%, 10%–<20%, and ≥20% under the variable of Census Tract Poverty Indicator in the PEDSF file. We used this variable as one of the measure of area-based socioeconomic status

❖ Low-income subsidy status (Also see **section 3.3.2.3** for more details): Whether an individual had received LIS will be based on the combined consideration of two variables in the Part D enrollment file: Cost Share Group (i.e., monthly indicators for beneficiary's LIS status) and State Reported Dual Eligible Status Code (i.e., monthly indicators for the dual Medicaid eligibility status, if any, for the beneficiary). Patients were defined as having a LIS if they received full or partial subsidy or were dually eligible for both Medicare and Medicaid (full or partial eligibility) at the month of their index date (i.e., date of NSCLC diagnosis). Three exposure groups were then created for the examination, including full LIS, partial LIS, and non-LIS. The definition of subsidy status is based on an established algorithm provided by the Research Data Assistance Center (ResDAC).[189,190]

❖ Health Status

- Charlson Comorbidity Index (CCI): Health status was measured using the Klabunde adaptation[191] of the CCI as approved by the National Cancer Institute. The adapted version contains the following main changes: First, the adapted version also considers diagnoses from the Medicare physician claims (Part B) to identify comorbid conditions, which aims to maximize the possibility of capturing important patient

comorbidities recorded on outpatient claims while more patients receive outpatient care than hospitalization. Second, a rule-out algorithm is applied to require any code in the physician claims should appear more than once and the code should appear again in either physician or inpatient claims after more than 30 days. This requirement aims to prevent overestimation of comorbidity. Last, the adapted version excludes cancer from the comorbidity index because cancer is the disease of interest, resulting 18 non-cancer conditions to be weighted for the adapted CCI. The refined measurement mentioned above helps enhance the measurement accuracy of comorbidities in claims data in cancer population. For this project, CCI was measured during the 6 months before the diagnosis date to capture baseline non-cancer comorbidities.

- Disability Status (DS)[192]: Predicted disability status (DS) was calculated based on a validated claims-based algorithm developed by Davidoff AJ et al. The estimation used physician, hospice, and durable medical equipment claims to include healthcare service use indicators (such as use of home oxygen, mobility aids, nursing home admission, or use of preventive services and elective surgical procedures) that are clinically relevant and prevalent among cancer population. This could serve as a proxy measure of performance status (PS), among older cancer population.

❖ Tumor characteristics

- Year and quarter of year: Although time at diagnosis does not directly impact patient outcomes, our study might be subject to the effect of longer-term observations from 2007-2013. These effects include advances in diagnosis and treatments, changes in treatment patterns, and natural disease progression (or care maturation). Thus, year of diagnosis, provided in the PEDSF file, will be categorized into 2007, 2008, 2009,

2010, 2011, 2012, or 2013 for each patient; quarter of the diagnosed year will be categorized into Q1 (January to March), Q2 (April to June), Q3 (July to September), or Q4 (October to December) based on the month of diagnosed made for the patient.

- Stage: Tumor stage in the PEDSF file is provided based on the 6th American Joint Committee on Cancer (AJCC) staging criteria. Our project focuses on locally advanced or metastatic cases. That is, stage IIIB and stage IV cases. Thus, we created a categorical variable to indicate a patient's cancer stage.
- Histology: Tumor histology was categorized according to ICD-O-3 histologic subtype codes in PEDSF file. We will include four categories: adenocarcinoma (8140-8147, 8250-8255, 8260, 8310, 8320, 8323, 8480-8481, 8490, 8510, 8550-8551, 8570-8576), squamous cell (8051-8078, 8083), large cell (8012-8015), and other/ not otherwise specified (NOS) (8003, 8004, 8020-8022, 8030-8035, 8046, and 8050, 8200-8201, 8230-8231, 8240-8246, 8249, 8980-8982, 8120-8124, 8430, 8560, 8562, 9050-9053). Other histological codes not representative of the NSCLC subtypes above was excluded from this study.

❖ Procedures

For this set of variables, the identification period would be from the diagnosis of NSCLC to the use of first anti-cancer medications for their advanced NSCLC. Due to concerns about possible sample size issues, we would not investigate into the distinct types of radiation or surgery procedures that may have been performed. Detailed information regarding the procedure codes are listed in **Appendix Table 3.5 and Appendix Table 3.6**.

- Radiation: An indicator variable was created based on the Medicare claims files, to denote whether the patient received radiation as part of the first course treatment.

- Cancer-directed Surgery: An indicator variable was created based on the Medicare claims files, to identify whether the patient received surgery as part of the first course treatment. Surgery of interest will include biopsy, local excision, and resection.

Table 3.5 Summary of Covariates at Baseline for Aim 2

Variable	Type	Definition	Source File
Demographic characteristics			
Age	Continuous & Categorical	Categorized as: 66-69; 70-79; 80+	PEDSF
Sex	Categorical	Male; Female	PEDSF
Race/ethnicity	Categorical	Non-Hispanic White; Non-Hispanic Black; Hispanic; Others	PEDSF
Marital status	Categorical	Single (never married), Married (including common law), Separated, Divorced, Widowed, Unmarried or domestic partner (same sex or opposite sex or unregistered), Unknown	PEDSF
Geographic characteristics			
Region	Categorical	Northeast, South, North Central, West, Other/Unknown.	PEDSF
Urban residence	Categorical	Big metro (Counties of metropolitan areas of 1 million population or more), Metro (counties in metropolitan areas of less than 1 million population), Urban (non-metropolitan counties with urban population of 20,000 or more), Less Urban (non-metropolitan counties with urban population of 2,500-19,999), Rural (non-metropolitan counties which are completely rural or with less than 2,500 urban population), and Unknown.	PEDSF
Institutional characteristic			
Institutional Affiliation	Binary	Ever received care from providers with affiliations, including the Eastern Cooperative Oncology Group (ECOG) (Yes/No), NCI cancer center designation, teaching hospital designation (Yes/No), or each level of affiliation with a medical school (Yes/No).	Provider file and MEDPAR and Outpatient files

Socioeconomic status			
Income – Median household income	Categorical	Aggregate census tract level measure of median household income	Census Tract file
Education – Percent 25 and older with < high school education	Categorical	Aggregate census tract level measure of education attainment	Census Tract file
Census Tract Poverty Indicator	Categorical	1= 0%-<5% poverty 2 = 5% to <10% poverty 3 = 10% to <20% poverty 4 = 20% to 100% poverty	PEDSF
Cost-sharing support status			
Low-income subsidy (LIS)	Categorical	Receipt of full LIS, partial LIS, or non-LIS at diagnosis	PEDSF
Health Status characteristics			
Charlson Comorbidity Index (Klabunde adaptation)	Continuous & Categorical	0; 1; 2+	MEDPAR, NCH, Outpatient
Disability Status (DS)	Categorical	Good (0-2); Poor (3-4)	NCH, DME, Hospice
Tumor-related characteristics			
Year of diagnosis	Categorical	2007; 2008; 2009; 2010; 2011; 2012; 2013	PEDSF
Quarter of the diagnosed year	Categorical	Q1 (January to March); Q2 (April to June); Q3 (July to September); Q4 (October to December)	PEDSF
Stage	Categorical	Stage IIIB; Stage IV	PEDSF
Histology	Categorical	Lung and bronchus cancer (International Classification of Diseases for Oncology, 3rd Edition, ICD-O-3, C34.0–C34.9) with ICD-O-3 histology: adenocarcinoma (8140-8147, 8250-8255, 8260, 8310, 8320, 8323, 8480-8481, 8490, 8510, 8550-8551, 8570-8576); squamous cell (8051-8078, 8083); large cell (8012-8015); other/ not otherwise specified (NOS) (8003, 8004, 8020-8022, 8030-8035, 8046, and 8050, 8200-8201, 8230-8231, 8240-8246, 8249, 8980-8982, 8120-8124, 8430, 8560, 8562, 9050-9053).	PEDSF
Procedures			
Radiation therapy	Dichotomous	Radiation as part of the first course treatment (Yes; No) **(See Appendix Table 3.5** for specific procedure codes**)**	PEDSF; MEDPAR, NCH

Cancer-directed surgery	Dichotomous	Surgery as part of the first course treatment (Yes; No) **(See Appendix Table 3.6** for specific procedure codes**)**	PEDSF; MEDPAR, NCH

Abbreviation: PEDSF, Patient Entitlement and Diagnosis Summary File; MEDPAR, Medicare Provider Analysis and Review File (i.e., Part A inpatient service); Outpatient, Part B institutional outpatient services; NCH, National Claims History File (i.e., Part B non-institutional outpatient services), HHA, Home Health Agency File (i.e., home health services), DME, Durable Medical Equipment File (i.e., durable medical equipment services) PDE, Prescription Drug Event file (i.e., Part D prescription drug dispensing).

3.2.2.4 Analysis

Descriptive statistics were first used to characterize both Part B and Part D treatment utilization and no treatment in the advanced NSCLC population. Changes in treatment patterns over time were assessed using the Chi-square test. Please note that, according to CMS, we are not allowed to show cell size less than 11. Therefore, the grouping in the results tables were changed accordingly.

Next, modified Poisson regressions were used to estimate the effect of each factor on the use of Part D drugs following 12 months of the advanced NSCLC diagnosis. Outcome of the model was the use of Part D drugs, a dichotomous variable defined as "ever use a Part D anti-cancer drug within 12 months after the diagnosis of advanced NSCLC" (versus never using a Part D drug). Because patients without any treatment within 12 months after diagnosis could be different from treated patients, we have another examination excluding these non-treated patients, comparing patients ever using a Part D anti-cancer drug with those only using Part B drugs within the 12 months since diagnosis. Bivariate examination was performed to understand the relationship between each independent variable and Part D drug use (i.e., crude estimates). Multivariate examination was then performed to include variables that are clinically and/or statistically important to Part D drug use (i.e., adjusted estimates). Risk ratios (RR) and corresponding 95% confidence intervals for each considered factors would be reported to

indicate the association between Part D medication use and the variable of interest (i.e., the relative risk of Part D drug use given exposure to the variable of interest).

All statistical tests are 2-sided, with a threshold of α=0.05 for statistical significance. All analyses will be performed in SAS 9.3 (SAS Institute, Cary NC).

3.3 AIM 3 – Evaluate the effect of low-income subsidies for Medicare Part D medications on treatment initiation among patients with advanced non-small cell lung cancer (NSCLC) from 2007 to 2014.

3.3.1 Data Source

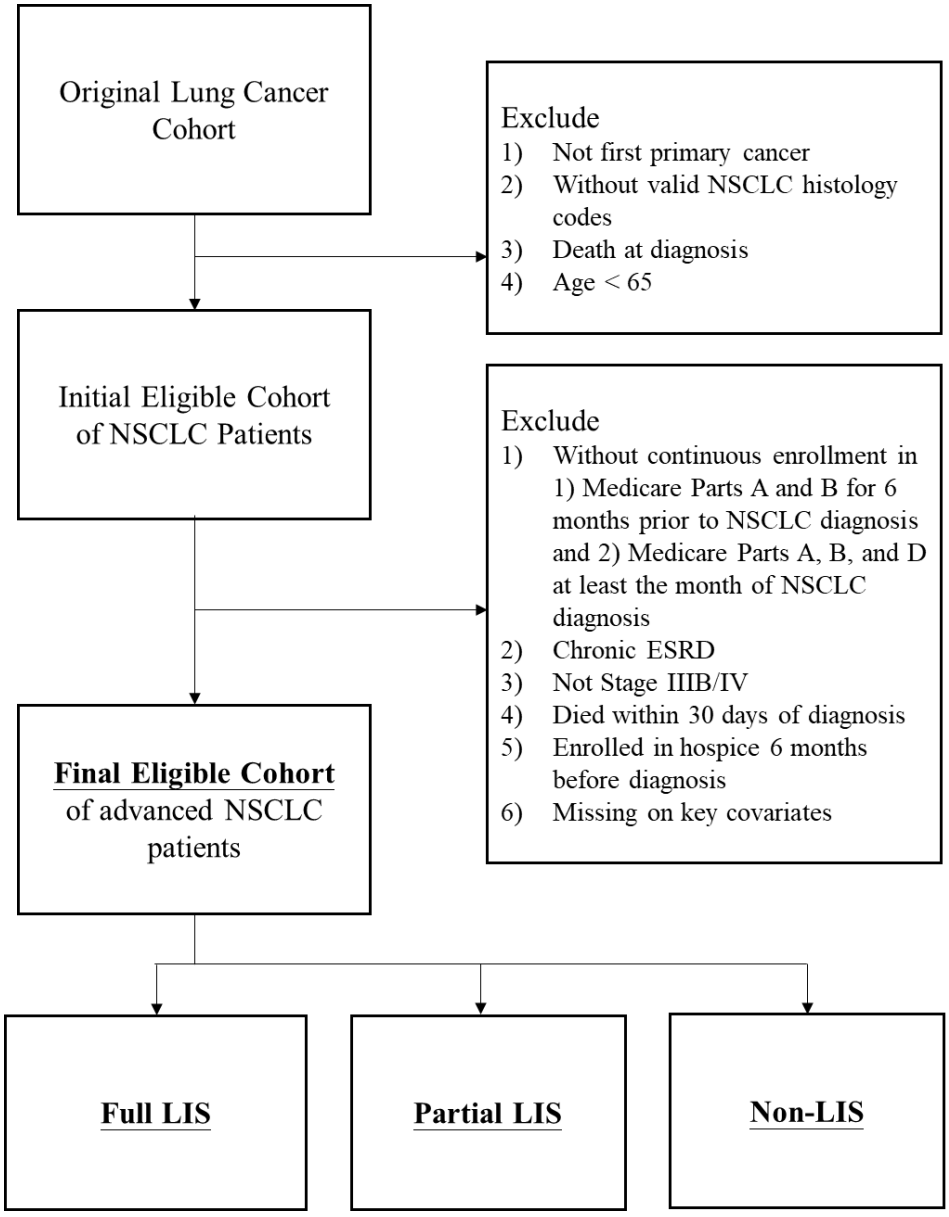
The SEER–Medicare database is used for this aim. Detailed description please see **section 3.2.1**.

3.3.2 Study Design

3.3.2.1 Cohort selection

Inclusion and exclusion criteria of study population were the same as Aim 2. Detailed description please see section 3.2.2.1. We further grouped the eligible cohort into 3 subgroups, including Full-LIS, Partial-LIS, and non-LIS groups (**Figure 3.5**). Detailed definition of LIS was provided in **section 3.3.2.3**.

Figure 3.5 Flow Diagram of Study Population Selection for Aim 3



Abbreviation: ESRD, end-stage renal disease; LIS, low-income subsidy; NSCLC, non-small cell lung cancer;

3.3.2.2 Exposure

To understand the effect of financial assistance on treatment uptake, our primary exposure is patients' low-income subsidy status (LIS) at the month of cancer diagnosis. Whether an individual had received LIS will be based on the combined consideration of two variables in

the Part D enrollment file: Cost Share Group (i.e., monthly indicators for beneficiary's LIS status) and State Reported Dual Eligible Status Code (i.e., monthly indicators for the dual eligibility status, if any, for the beneficiary). Dual Eligible Status is considered because with concurrent enrollment in Medicaid or Medicare Savings Programs (e.g., Qualified Medicare Beneficiary Program (QMB), Specified Low-Income Medicare Beneficiary Program (SLMB), or Qualified Individual Program) (QI)), where state programs pay Medicare Part B premiums, one will automatically qualify to get help paying for Medicare prescription drug coverage. Therefore, patients were defined as having a LIS if they received full or partial subsidy or were dually eligible for both Medicare and Medicaid (full or partial eligibility) at the month of their index date (i.e., date of NSCLC diagnosis). Three exposure groups were then created for the examination, including full LIS, partial LIS, and non-LIS. That is, a patient would be assigned to full LIS group if either one of the two indicators at the month of diagnosis is shown as full. The rest of the patient would then be grouped into partial LIS group if either one of the two indicators at the month of diagnosis is shown as partial. Lastly, the rest of the patients would fall into non-LIS group. The definition of subsidy status is based on an established algorithm provided by the Research Data Assistance Center (ResDAC).[189,190]

We categorized people into three LIS groups based on the following rules: a patient would be assigned to Full LIS group if either one of the two indicators at the month of diagnosis is shown as Full. The rest of the patient would then be grouped into Partial LIS group if either one of the two indicators at the month of diagnosis is shown as Partial. Lastly, the rest of the patients will fall into non-LIS group.

Please also see **Table 2.1** for the eligibility and cost-sharing for Medicare Part D benefit for each low-income subsidy groups.

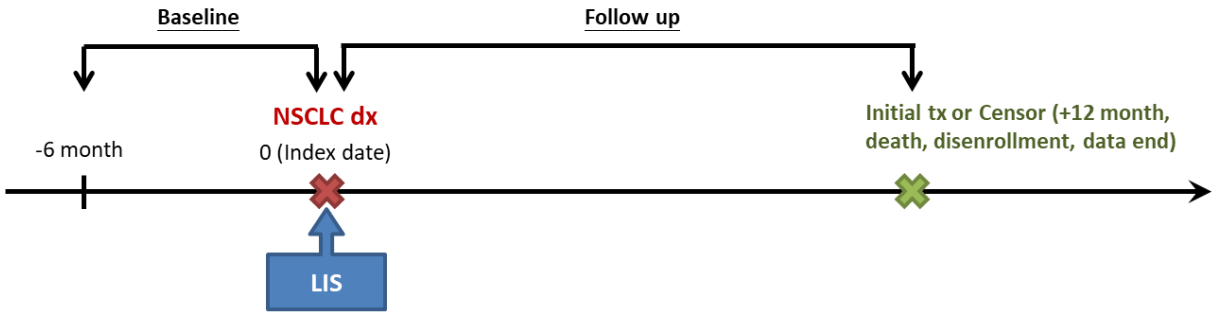
3.3.2.3 Outcome Measurement

Initial access to treatment is particularly important for those who are newly diagnosed with cancer, where prompt treatment is often essential. This aim examines uptake and timing of anticancer medications (separately for Medicare Part B and Medicare Part D). The key outcome of interest was the timing of anticancer medications initiation.

Drugs of interest were Part D and Part B drugs with United States Food and Drug Administration approval for advanced NSCLC by the end of 2014 **(Table 3.1 and Table 3.2)**. Part D drugs were the primary focus for the examination. In addition, Part B drugs would serve as a negative control for a robustness check, in which no effect of LIS status is expected on the time to initiation, since most Medicare beneficiaries have supplemental coverage for Part B treatments.

To identify the use, patients were followed starting from the date of being diagnosed with advanced NSCLC until they initiated a Part D NSCLC treatment, or being censored (i.e., through the date of death from any cause, disenrollment, the 12^{th} month, or the end of data since diagnosis). Outcome of interest is the time to receive first Part D drug treatment since diagnosis, counted as the period of days between the date of advanced NSCLC diagnosis and first receiving the treatment of interest. (**Figure 3.6)**.

Figure 3.6 Study Design for Aim 3



[a] The study design includes a six-month period prior to the diagnosis of NSCLC to measure the baseline patient characteristics. We followed patient from the diagnosis until death, disenrollment, the 12th month since diagnosis, or the end of data (December 31, 2014), whichever occurred first. This post-diagnosis period was used to identify the outcomes of interest.

3.3.2.4 Covariates

Covariates considered are the same as Aim 2, except that Low-income subsidy status serves as the exposure of interest for Aim 3. A six-month period prior to the diagnosis of NSCLC to measure the baseline patient characteristics. Detailed descriptions of the covariates please see section **3.2.2.3**.

3.3.3.5 Analysis

We first described baseline characteristics of the study population, with respect to their demographic, geographic, clinical, and institutional characteristics, stratified by LIS status at the month of NSCLC diagnosis. Chi-square tests and t-tests were used to compare group difference in categorical and continuous variables considered, respectively. This step aims to understand potential underlying differences between those who received LIS and those who did not.

Second, Kaplan-Meier curves were generated to compare the unadjusted timing of Part D medication use among full LIS, partial LIS, and non- LIS populations. In addition, Cox proportional hazards model were applied for covariate adjustment in the comparison of the

treatment timing of initiation among the three LIS groups.

Inverse Probability of Treatment Weight[193]

Given the differences among those who received LIS and those who did not, we additionally applied inverse probability of treatment weight (IPTW) in the models to adjust for the imbalance of patient characteristics among LIS groups. To calculate the IPTW, we first used a logistic regression to estimate the propensity score by predicting LIS status as a function of the following covariates: patient demographic (age, sex, marital status, race/ethnicity), geographic characteristics (SEER region, urban residence), institutional characteristics (whether the patient ever receive care from providers in affiliations with: the Eastern Cooperative Oncology Group (ECOG), NCI cancer center designation, teaching hospital designation, or level of affiliation with a medical school), socioeconomic status (census tract level of education, poverty, and median household income), health status (Klabunde's adaptation of the Charlson comorbidity index, predictd Disability Status), tumor-related characteristics (stage, histology, time of diagnosis), and receipt radiation or surgery as part of the first course treatment **(**See **Table 3.5** for complete list of variables considered**)**.

Next, we created IPTW for each patient using the inverse of the propensity score. These were equal to 1/p (where p is the propensity score). We further stabilized the propensity score weights by multiplying the IPTW weights by the marginal prevalence of the treatment they received. The resulting IPTW were used to reduce selection bias and better clarify the effect of LIS status.

Hazard Ratios and corresponding 95% confidence intervals were provided to indicate the relative likelihood of initiating Part D medication in three LIS groups (i.e., non-LIS, partial LIS, and full LIS as reference).

All statistical tests are 2-sided, with a threshold of α=0.05 for statistical significance. All analyses will be performed in SAS 9.3 (SAS Institute, Cary NC).

3.3.3.6 Sensitivity Analysis

In our primary analysis, we want to isolate the effect of high out-of-pocket spending on treatment uptake using LIS as a marker for treatment affordability. However, patients who qualify for LIS are financially disadvantaged relative to their non-LIS peers and may face additional challenges starting and managing their medication use. To better understand the relationship between out-of-pocket costs and treatment uptake we selected a negative control scenario to explore the relationship between LIS and treatment initiation when out-of-pocket spending is expected to be low for both LIS and non-LIS groups. We used Part B medication uptake as our negative control scenario because supplemental health insurance options are available for beneficiaries to pay the cost-sharing requirements for the services under Part B, including deductibles, copayments, and coinsurance. This supplemental coverage results in lower, more consistent and predictable expenses for patients using Part B services throughout the year. According to Kaiser Family Foundation, more than 80% of fee-for-service Medicare beneficiaries have some source of supplemental coverage.[7]

CHAPTER FOUR: RESULTS

4.1 AIM 1– Examine changes in drug-specific price, formulary structure, and the use of utilization management tools for Part D medications approved for advanced NSCLC from 2009 to 2017.

In this aim, we hypothesized that 1) over time Part D drug prices have increased over the study period in addition to inflation; 2) over time advanced NSCLC medications covered under Part D are more likely to be placed on the highest drug tier or specialty drug tier within the formulary; 3) over time advanced NSCLC medications covered under Part D are more likely to require coinsurance (rather than copayments) for calculating patient cost-sharing; and 4) Over time advanced NSCLC medications covered under Part D are more likely to be subject to utilization management (e.g., step therapy, prior authorization, quantity limits).

Drug Prices for Products Covered Under Medicare Part D

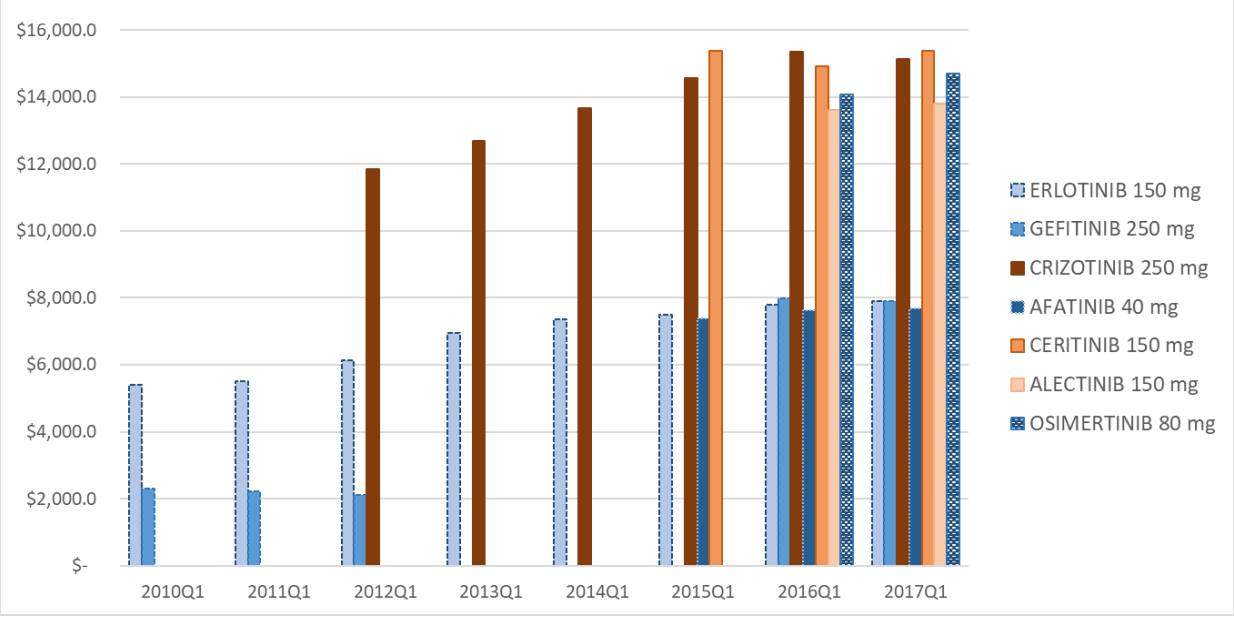
Prices for all advanced NSCLC drugs covered under Part D have increased over the study period (**Figure 4.1**). Over time, prices have increased from an average of 3,851/month in 2010Q1 to $9,996/month in 2017Q1. For individual products, prices in the most recent quarter ranged from $5,109/month (for erlotinib) to $15,384/month (for ceritinib) **(Figure 4.1, Appendix Table 4.1)**.

Over time we observe higher initial prices for approved treatments and growing prices for existing products. For example, the most recently approved drug, alectinib, was priced at around

$14,000/month at approval **(Figure 4.1, Appendix Table 4.1)**. Whereas, the prices asked for older drugs (e.g., erlotinib) were below $5,000/month. Given the fact, its price has still increased by almost 50% during the study period.

Gefitinib, the oldest tyrosine kinase inhibitor approved for advanced NSCLC, had limited use in the U.S. since 2005 because of disappointing trial results[194] and was not covered under any Part D plans between 2013Q1 and 2015Q1 due to withdrawal[195] **(Figure 4.1, Appendix Table 4.1)**. Since 2015, gefitinib coverage has improved based on new evidence of its role in the treatment for individuals with EGFR mutations. In 2010Q1 this drug was priced at $2,296/month but more recently the price has increased to $7,898/month.

Figure 4.1 Median Prices of Advanced Non-Small Cell Lung Cancer Drugs Covered under Part D (2017 USD)[a,b]

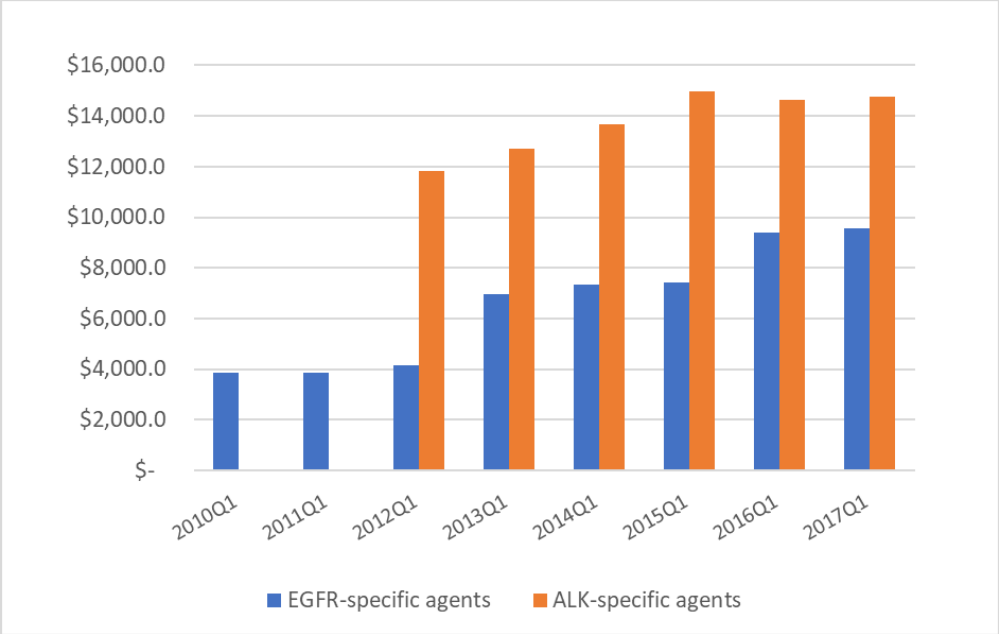


[a] Only one dosage form within each drug were presented in the figure. Dosage form were selected if the dose per pill matches the dose per uptake recommended in the NCCN guideline.
[b] Blue-shaded colors represent EGFR targeted agents and orange-shaded colors represent ALK-targeted agents.

When we consider drug prices at the therapeutic class level, we see somewhat different trends. There are two primary drug classes among drugs used for NCSLC and covered under Medicare Part D in our study period, including ALK-targeted drugs and EGFR-targeted drugs. We observed that ALK targeted drugs were priced much higher at the time of FDA approval (over $12,000/month) as compared to EGFR-targeted drugs (below $5,000/month) **(Figure 4.2)**. This might be because ALK targeted agents are a relatively newer therapeutic class at the time and the prevalence of ALK is small (less than 10%). On average, the price asked for ALK-targeted agents had been 1.5 to 3 times higher than the price for EGFR-targeted agents ($11,843 vs. $4,135/month in 2012Q1 and $14,769 vs. $9550/month in 2017Q1) **(Figure 4.2, Appendix Table 4.1)**. However, osimertinib, the newest EGFR-targeted drug which was approved in 2015, was priced at comparable price for ALK-targeted agents for more than $14,000/month (**Figure 4.1, Appendix Table 4.1**).

Interestingly, we observed that different dosage forms of a drug were priced at similar level or with minimal difference **(Appendix Table 4.1)**. For example, there is less than $60 difference in the price (both mean and median) between afatinib 20mg and 40mg over time. An identical price, over $14,000/month, was even set for osimertinib in both 40mg and 80mg formulations since its approval.

Figure 4.2 Average Price of Advanced Non-Small Cell Lung Cancer Drugs Covered under Part D, by Therapeutic Class (2017 USD)[a]

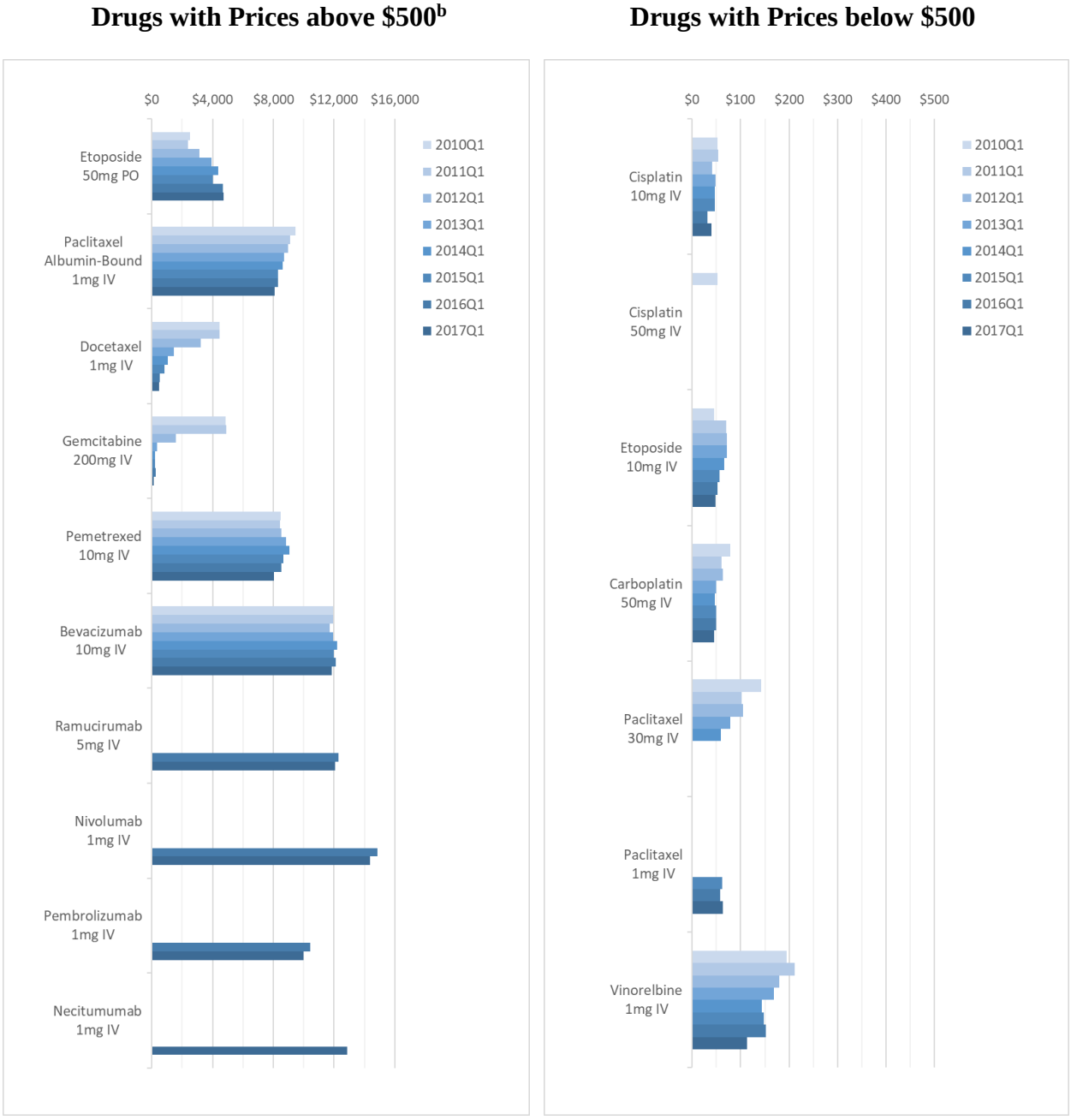


[a] Only one dosage form within each drug were selected (if the dose per pill matches the dose per uptake recommended in the NCCN guideline) for the average price calculation.

Drug Prices for Products Covered Under Medicare Part B

In contrast to trends observed among drugs covered under the Medicare Part D benefit, Part B drug prices have been stable over the past 8 years **(Figure 4.3, Appendix Table 4.2)**. Most of the traditional chemotherapies were off patent and have generics available during the study period; the prices were consistently low at below $100/month (e.g., platinum-based agents) or dropped considerably by up to 80% in the year when generic versions were approved (e.g., docetaxel, gemcitabine). Traditional agents in new formulations were still under patent protection with prices consistently high above $8,000/month (e.g., albumin-bound paclitaxel) and even increasing by 88% over the period examined, from $2,513 in 2010 to $4,728 in 2017 (e.g., oral etoposide). A relatively newer infused chemotherapy, pemetrexed, had also been priced above $8,000/month since 2010.

Figure 4.3 Average Sales Prices for Advanced NSCLC Drugs Covered under Part B (2017 USD)[a]

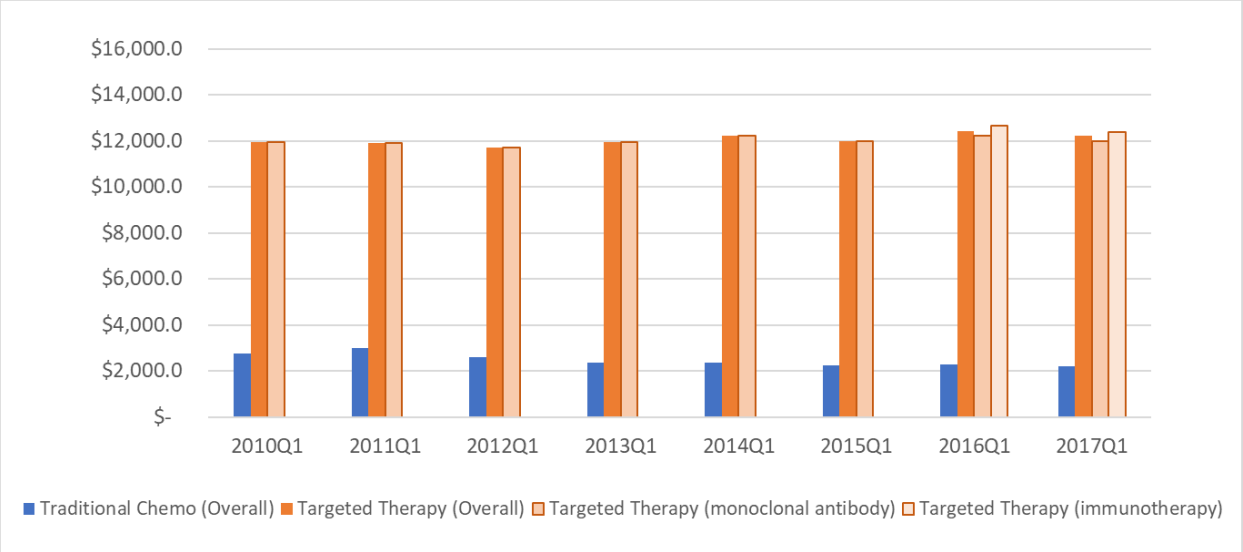


[a] Please see **Appendix Table 4.2** for more details in Average Sales Prices for Part B drugs.

[b] The Average Sales Prices of docetaxel 1mg IV and gemcitabine 200mg IV declined to below $500/month since 2017 and 2013, respectively. In 2017, the price of docetaxel 1mg IV was $499.0/month and the price of gemcitabine 200mg IV was $144.5/month.

Novel targeted therapies covered under Part B were priced above $10,000 for a month of treatment at the time of first FDA approval for advanced NSCLC. Even the drug with the earliest indication for NSCLC, bevacizumab, which was approved in 2006, was priced at almost $12,000/month in 2010 and at similar level afterwards. The price for the most recent approved immunotherapies could be more than $14,000/month (e.g., nivolumab). On average, the price of novel targeted treatments was 5.6 times higher than the price of traditional chemotherapies; among novel treatments, immunotherapies were priced more than $400 higher compared to the prices for monoclonal antibodies. **(Figure 4.4)**.

Figure 4.4 Average Sale Prices of Advanced Non-Small Cell Lung Cancer Drugs Covered under Part B, by Therapeutic Class (2017 USD)[a,b]



[a] Blue-shaded colors represent traditional chemotherapies; orange-shaded colors represent targeted therapies and its subgroups.
[b] Targeted therapy (overall) include both monoclonal antibodies treatments and immunotherapies.

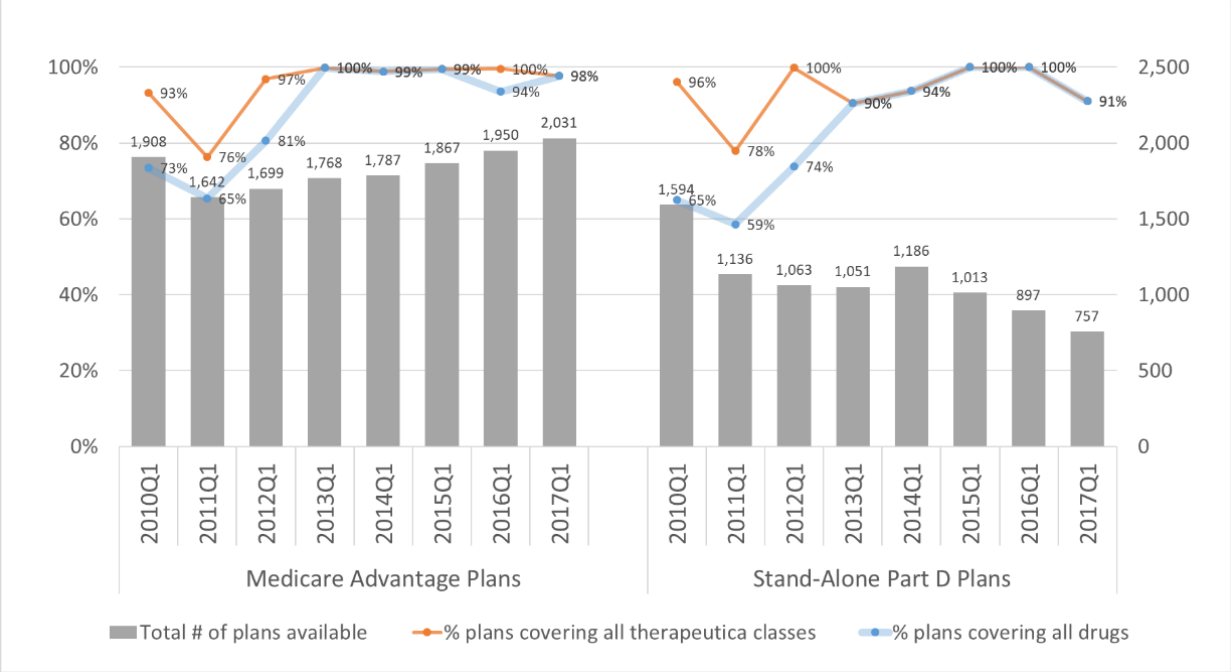
Coverage Design and Formulary Structure

Across years, the overall number of Medicare prescription drug plans available to seniors has decreased **(Figure 4.5, Appendix Table 4.3)**. Decreases have occurred mainly in the category of stand-alone prescription drug plans (PDPs) rather than in the Medicare Advantage

prescription drug plans (MA-PDs). Stand-alone plans are typically offered to enrollees in traditional Medicare (about 70% of all Medicare enrollees) and Medicare Advantage plans are offered in private plans (about 30% of all Medicare enrollees).[6] The number of PDPs declined by 53% from 1,594 to 757 plans between 2010Q1 and 2017 Q1. A considerable drop in number of plans (14% in MA-PDs and 29% in PDPs) was observed in 2011Q1.

Among the available plans in each year (except 2011Q1), more than 90% of them covered at least 1 advanced NSCLC drug in each therapeutic class. Since 2013Q1, more than 90% of the plans covered all advanced NSCLC drugs available at the time. In 2017Q1, 98% of the MA-PDs and 91% of the PDPs provide coverage for all advanced NSCLC drugs on the market.

Figure 4.5 Part D Plan Coverage for Advanced Non-Small Cell Lung Cancer Care, by Plan Type, 2010Q1 to 2017Q1

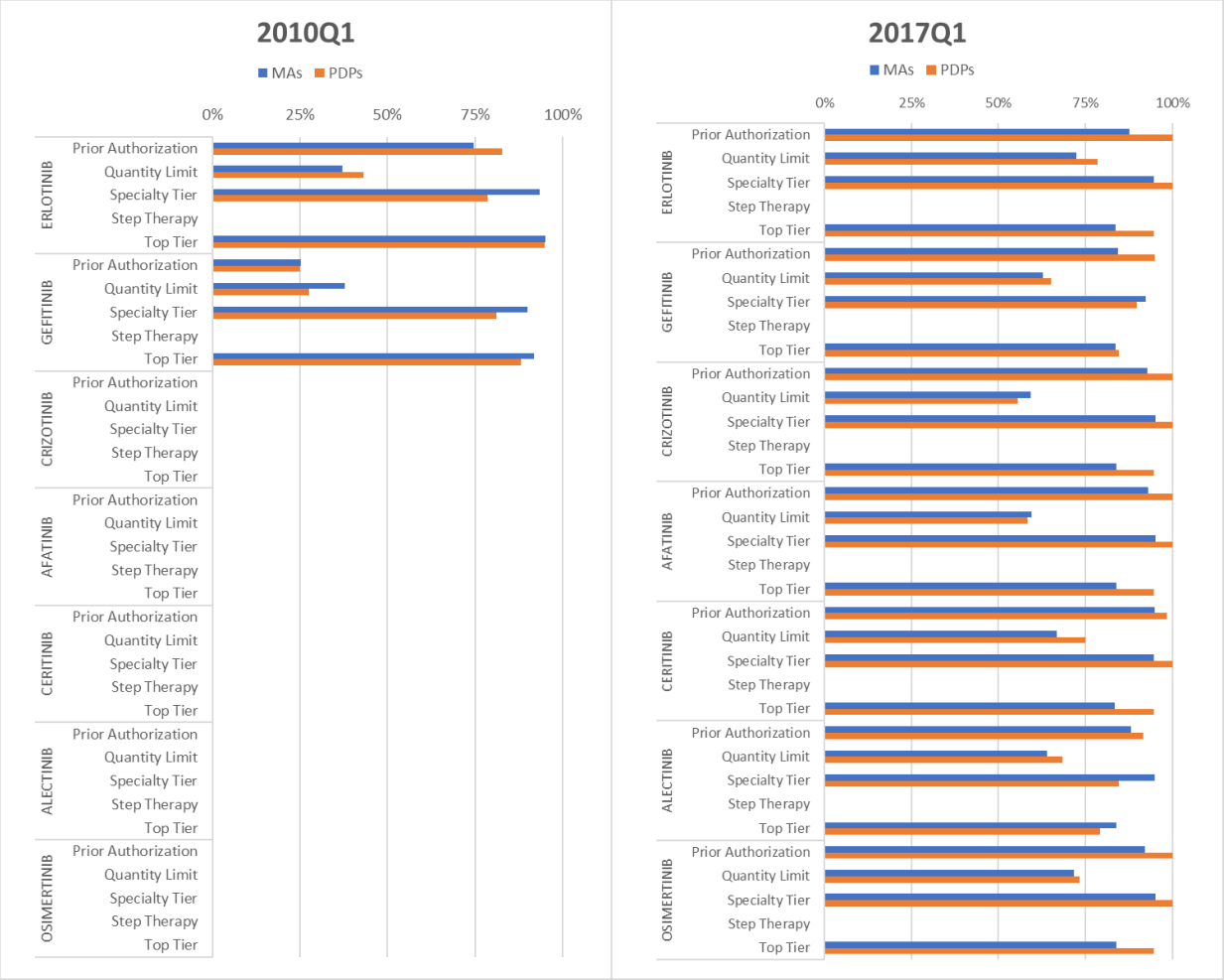


In terms of the application of utilization management tools, MA-PDs were less likely than PDPs to apply prior authorization and quantity limits to advanced NSCLC drugs across

years. An increase was observed in the use of both tools, particularly for older drugs that have been available since mid-2000s (e.g., erlotinib, gefitinib) **(Figure 4.6, Appendix Table 4.4)**. On the other hand, step therapy requirements were rarely used by plans. In 2017, utilization management tools were applied in a similar manner across available drug treatments (prior authorization use: 85-95% MA-PDs and 92-100% PDPs; quantity limits: 59-72% MA-PDs and 55-79% PDPs; step therapy: 0% in both MA-PDs and PDPs).

In terms of the drug tiering, PDPs were more likely to assign top tiers or specialty tiers to advanced NSCLC drugs as compared to MA-PDs across years although more than 80% of both types of plan applied the tiering **(Figure 4.6)**. Particularly in 2017Q1, 5 out of the 7 drugs available for treating advanced NSCLC were in specialty tiers across all plans.

Figure 4.6 Utilization Management Tools and Formulary Tiering in Advanced Non-Small Cell Lung Cancer Drugs, 2010Q1 vs. 2017Q1[a]

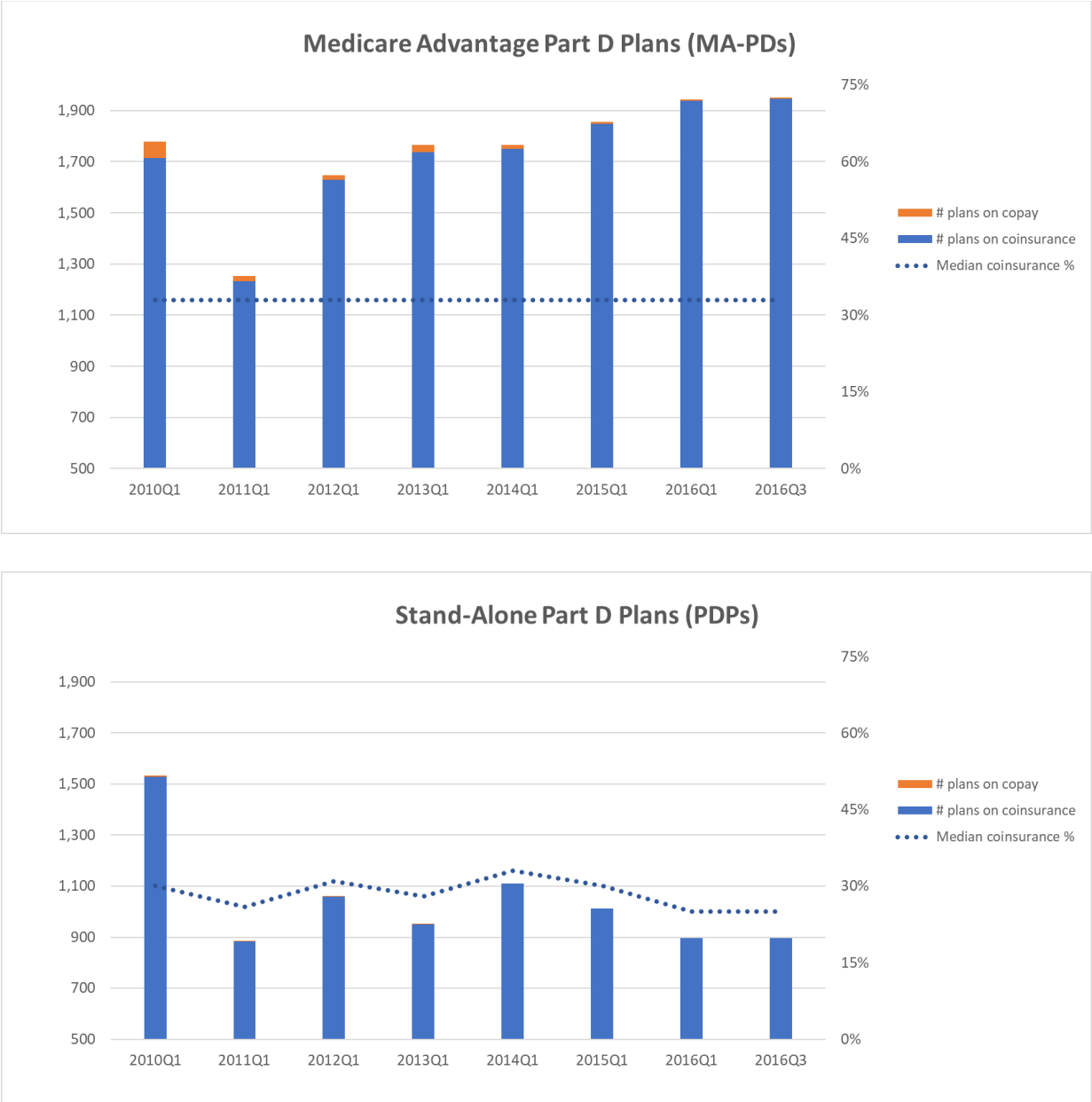


[a] Each bar in the figure represents proportion of plans applying the measures among all plans that covering the drug.

Cost-sharing requirement for approved NSCLC treatments have changed only slightly over the study period. Almost all plans required coinsurance for using each advanced NSCLC drug treatment in the initial coverage phase of the Part D benefit across each year. Between 2010Q1 and 2016Q3 (the most recently available complete data) the median coinsurance applied to drugs was 33% (IQR: 25-33% for both MA-PDs and PDPs). Similarly, in catastrophic phase, most of the plans applied co-insurance (in 2017Q1, 98.2% in MAs and 100% in PDPs), at

consistent 5% amount, for each drug treatment across each year. **Figure 4.7** shows the cost-sharing requirement for erlotinib as an example.

Figure 4.7 Trend of Cost-Sharing Requirement for Erlotinib on Medicare Part D Formularies in the Initial Coverage Phase, 2010Q1 - 2016Q3[a,b]

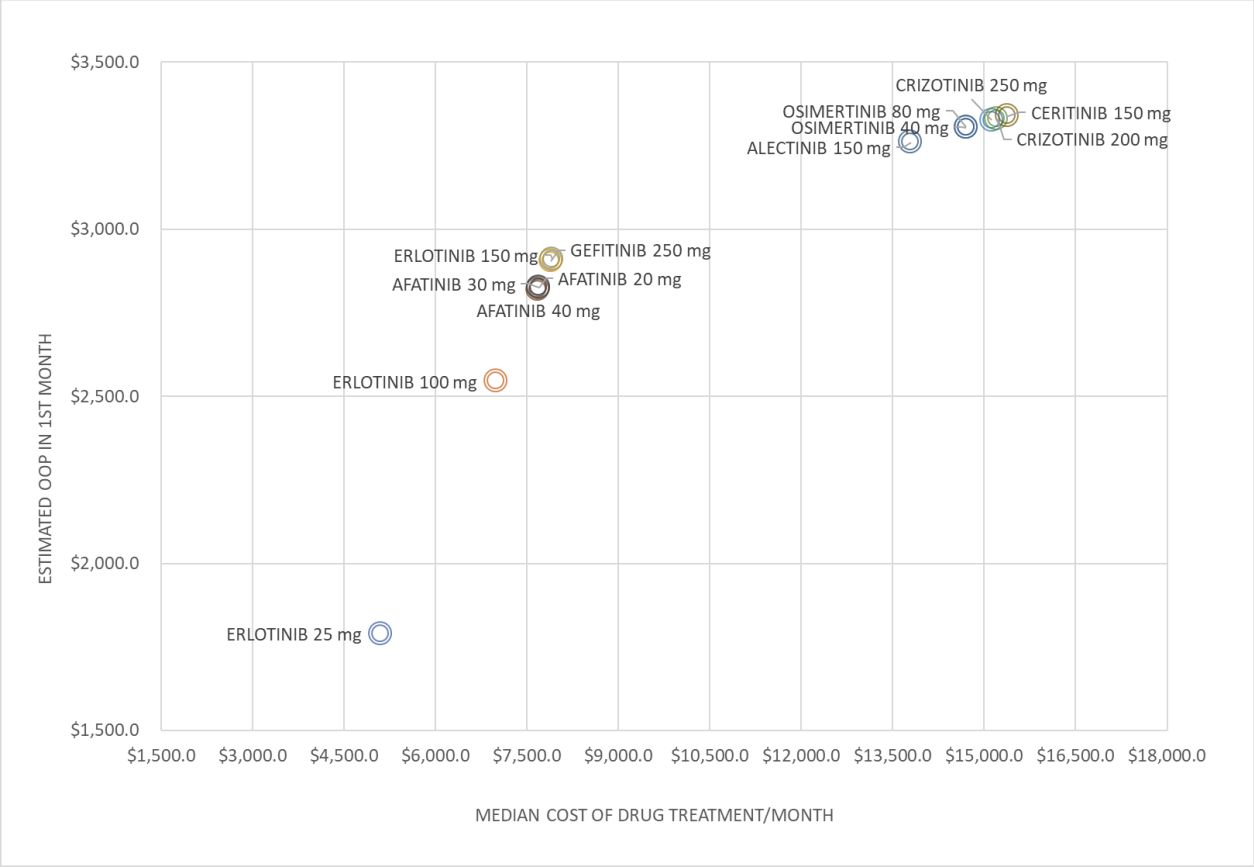


[a] Due to missing data on cost-sharing in initial coverage phase in 2016Q4 and 2017Q1, we used the most recent and complete data for this examination.
[b] The left axis denotes the total number of plans each year; the right axis denotes the median amount of coinsurance (i.e., percentage of the drug cost) required by plans during a year.

Out-of-Pocket Spending Estimates for Medicare Part D Covered Drugs

Given the high prices and cost-sharing requirement by Part D plans, patient out-of-pocket cost (OOP) could be several thousand dollars for initiating a Part D drug treatment for advanced NSCLC. For a non-LIS patient enrolled in a plan with standard Part D benefits in 2017, the OOP could be more than $2,500/month for drugs with the most commonly used dosage **(Figure 4.8)**. For the most recently approved drugs, the initiating cost of using could be $3,300/month (e.g., osimertinib of EGFR-targeted agents and alectibnib of ALK-targeted agents).

Figure 4.8 Estimated First-Month Out-of-Pocket Cost (OOP) of Advanced Non-Small Cell Lung Cancer Part D Drug Treatments in 2017 [a]



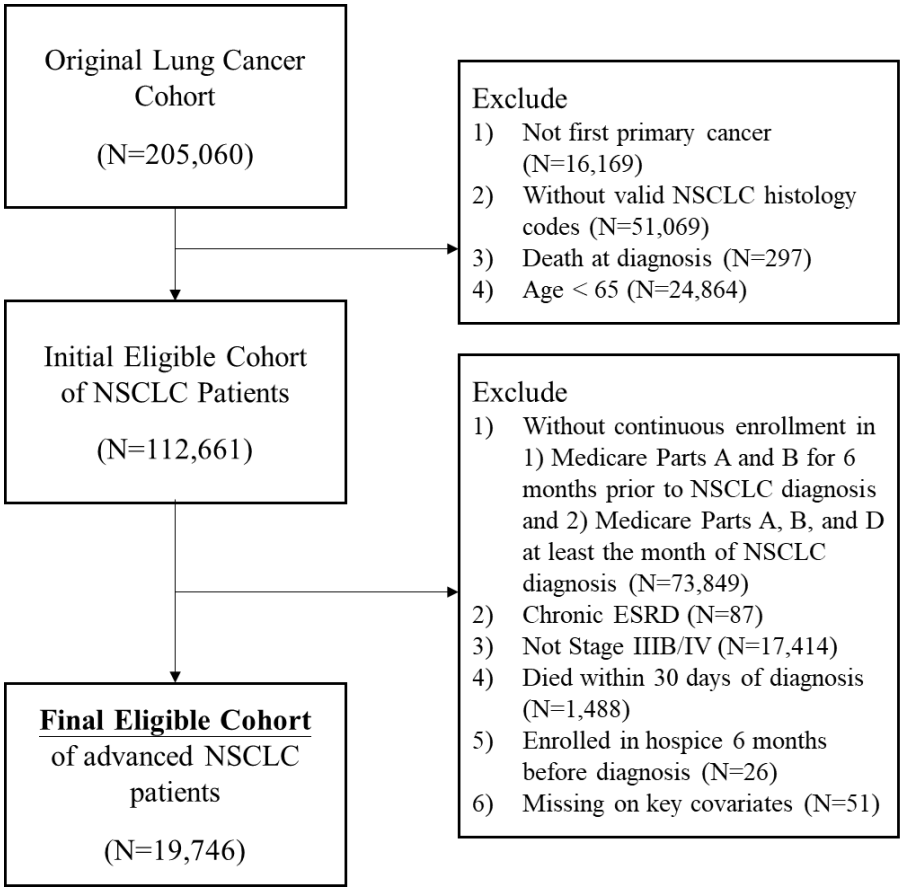
[a] This estimation was based on each drug's median cost per month in 2017. We calculated the out-of-pocket costs (OOP) for a non-LIS patient enrolled in a plan with standard Part D benefits in 2017 with the assumption that the patient had no prior OOP expense in Part D prior to the advanced NSCLC treatment.

4.2 AIM 2– Examine trends in the utilization of advanced NSCLC medications by coverage source (i.e., Medicare Part B or Part D). In addition, to identify clinical, sociodemographic, and health system factors associated with the use of Part D treatments among patients diagnosed with advanced NSCLC from 2007 to 2014.

In this aim, we hypothesized that: 1) the use of advanced NSCLC medications covered under Part D has increased over the study period; and 2) the use of advanced NSCLC medications covered under Part B has decreased over the study period.

To derive a NSCLC cohort **(Figure 4.9)**, all patients in the SEER database with a primary cancer of the lung and bronchus diagnosed between July 1, 2007 and December 31, 2013 were initially selected (N=205,060). Subsequently, we excluded patients for whom lung cancer was not their first primary cancer and patients without valid NSCLC histology codes, those died at diagnosis, and those aged equal or older than 65, which resulted in an initial eligible cohort of 112,661 NSCLC patients. After further applying additional selection criteria for continuous enrollment in Medicare, health status (e.g., hospice enrollment, death within 30 days of diagnosis, chronic ESRD or not), and the completeness of data we obtained the final eligible cohort of 19,746 advanced NSCLC patients.

Figure 4.9 Flow chart of the study population selection



Abbreviation: ESRD, end-stage renal disease; NSCLC, non-small cell lung cancer.

The final advanced NSCLC cohort diagnosed between July of 2007 and December of 2013 were on average 75.1 years old (SD: 6.8) **(Figure 4.9, Table 4.1)**. Mean comorbidity scores were 1.2 (SD 1.5; 70.0% with scores 0-1) and more than 90% of the patients had good predicted Disability Status (DS, a claim-based proxy measure of performance status[192] at baseline). Among them, 49% were male and more than 75% were non-Hispanic Whites. Adenocarcinoma and squamous subtypes consisted of 51.7% and 26.5% of the patient tumor histology, respectively. In respect of socioeconomic status, more than 80% of the patients lived in metro areas of 1 million or more population (i.e., Big Metro or Metro areas). When considering census tract level characteristics, 30.7% of the patients lived in areas with more than

20% of the population without high school diploma. In addition, more than a quarter (28.7%) of the patients lived in areas with more than 20% of the residents living below poverty and 40.3% of the patients received partial or full low-income subsidy for Medicare Part D prescription drug coverage.

Based on the drug use within 365 days of diagnosis of advanced NSCLC, we observe four treatment groups, use of both Part B & D drugs, only Part D drug use, only Part B drug use, and never use of Part B or Part D drugs **(Table 4.1A)**. Patients who did not receive treatment within 365 days of diagnosis accounted for 49.7% of the total advanced NSCLC population. Compared to other treated groups, they were less likely to be married (33.7%), appeared to live in poorer areas (63.1% living in census tract with more than 20% residents below poverty level) or areas with lower education level (64.1% living in census tracts with more than 10% residents without High School Degree). Among this group, 41.8% received full LIS (vs 35.3% of all NCSLC patients). In terms of health status, these patients appeared to have the highest levels of comorbidity (34.3% with Comorbidity Score of 2 or more) and were more likely to have a poor Disability Score (14% with score of 3-4), in comparison to other treated groups. In addition, these patients were also much less likely to receive care from hospitals designed as NCI centers, teaching hospital, or with major affiliation with medical school.

Patients who used only Part D drugs (versus other patients receiving any drug-based therapy) were older (more patients aged 80 or over: 45.4% for Part D drug only vs. 19.2% for both Parts D &B drugs vs. 14.8% for Part B drug only), most likely to be women (66.8% vs. 55.6% vs. 47.4%), and had more than a quarter of the patients in “Other” race/ethnicity group (28.9% vs. 17.0% vs. 5.6%). In addition, more than half of the Part D only group lived in the

West region (56.8% vs. 49.5% vs. 36.0%) and almost 90% lived in Metro or Big Metro areas (88.7% vs. 82.2% vs. 79.2%).

Socioeconomic status was similar across treated groups; about 57% of the patients lived in census tracts where more than 10% of residents had no High School Degrees and about 25% residing in census tracts with more than 20% of residents living below poverty level. Patients treated with only Part D drugs were most likely to receive full LIS (45.8% vs. 32.4% vs. 26.7%) while those treated with only Part B drugs were least likely to receive any level of LIS.

In terms of health status, patients receiving Part D drugs only were most likely to have poor Disability Scores (8.6% vs. 2.5% vs. 3.8%) while the Part B drug only group was most likely to have Comorbidity Score of 1 or more (51.8% vs. 50.2% vs. 55.3%). Compared to Part B drug only group, those who ever received a Part D drug were more like to be diagnosed with stage IV cancers (76.2% vs. 69.8%) and more likely to have adenocarcinoma histology (71.5% vs. 49.7%). In terms of the other treatments, Part B drug only groups were most likely to receive radiation or surgery as part of their first course of treatment.

Table 4.1A Patient Characteristics at Baseline (N=19,746)

		Grand Total		Use both Part B & D drugs use within 365 days		Use only Part D drugs within 365 days		Use only Part B drugs within 365 days		No Part B or D drugs use within 365 days		
		N=19746		N=1017		N=1019		N=7906		N=9804		
		N	%	N	%	N	%	N	%	N	%	p-value
Age												<.0001
	65-69	4733	24.0%	301	29.6%	143	14.0%	2413	30.5%	1876	19.1%	
	70-74	5375	27.2%	284	27.9%	189	18.5%	2558	32.4%	2344	23.9%	
	75-79	4433	22.5%	237	23.3%	224	22.0%	1766	22.3%	2206	22.5%	
	80+	5205	26.4%	195	19.2%	463	45.4%	1169	14.8%	3378	34.5%	
Sex												<.0001
	Male	9745	49.4%	452	44.4%	338	33.2%	4162	52.6%	4793	48.9%	
	Female	10001	50.6%	565	55.6%	681	66.8%	3744	47.4%	5011	51.1%	
Race/Ethnicity												<.0001
	Non-Hispanic White	14929	75.6%	705	69.3%	591	58.0%	6350	80.3%	7283	74.3%	
	Non-Hispanic Black	2025	10.3%	73	7.2%	62	6.1%	702	8.9%	1188	12.1%	
	Hispanic	1151	5.8%	66	6.5%	71	7.0%	409	5.2%	605	6.2%	
	Others	1641	8.3%	173	17.0%	295	28.9%	445	5.6%	728	7.4%	
Marital Status												<.0001
	Married	8903	45.1%	581	57.1%	475	46.6%	4191	53.0%	3656	37.3%	
	Single	10092	51.1%	405	39.8%	510	50.0%	3445	43.6%	5732	58.5%	
	Unknown	751	3.8%	31	3.0%	34	3.3%	270	3.4%	416	4.2%	
Region												<.0001
	North East	3765	19.1%	174	17.1%	183	18.0%	1599	20.2%	1809	18.5%	
	South	5746	29.1%	247	24.3%	189	18.5%	2353	29.8%	2957	30.2%	
	North Central	2571	13.0%	93	9.1%	68	6.7%	1106	14.0%	1304	13.3%	
	West	7664	38.8%	503	49.5%	579	56.8%	2848	36.0%	3734	38.1%	
Urban/Rural Residence												<.0001
	Big Metro	10188	51.6%	557	54.8%	653	64.1%	4000	50.6%	4978	50.8%	
	Metro	5694	28.8%	278	27.3%	251	24.6%	2279	28.8%	2886	29.4%	
	Urban	1227	6.2%	70	6.9%	46	4.5%	523	6.6%	588	6.0%	
	Less Urban	2125	10.8%	93	9.1%	64	6.3%	869	11.0%	1099	11.2%	
	Rural	512	2.6%	19	1.9%	5	0.5%	235	3.0%	253	2.6%	
Census Tract % of without High School Degree												<.0001
	00-05%	3114	15.8%	209	20.6%	213	20.9%	1337	16.9%	1355	13.8%	
	05-10%	4621	23.4%	241	23.7%	230	22.6%	1984	25.1%	2166	22.1%	

	10-20%	5953	30.1%	262	25.8%	266	26.1%	2370	30.0%	3055	31.2%	
	20-100%	6058	30.7%	305	30.0%	310	30.4%	2215	28.0%	3228	32.9%	
Census Tract % below poverty												<.0001
	00-05%	3303	16.7%	211	20.7%	205	20.1%	1471	18.6%	1416	14.4%	
	05-10%	4672	23.7%	258	25.4%	253	24.8%	1957	24.8%	2204	22.5%	
	10-20%	6109	30.9%	293	28.8%	308	30.2%	2439	30.8%	3069	31.3%	
	20-100%	5662	28.7%	255	25.1%	253	24.8%	2039	25.8%	3115	31.8%	
Census Tract Household Median Income												<.0001
	1st Quartile	4936	25.0%	222	21.8%	185	18.2%	1749	22.1%	2780	28.4%	
	2nd Quartile	4937	25.0%	220	21.6%	224	22.0%	2008	25.4%	2485	25.3%	
	3rd Quartile	4936	25.0%	252	24.8%	261	25.6%	2025	25.6%	2398	24.5%	
	4th Quartile	4937	25.0%	323	31.8%	349	34.2%	2124	26.9%	2141	21.8%	
Receipt of Low Income Subsidy (LIS)												<.0001
	Full LIS	6979	35.3%	329	32.4%	467	45.8%	2112	26.7%	4071	41.5%	
	No LIS	11778	59.6%	654	64.3%	513	50.3%	5427	68.6%	5184	52.9%	
	Partial LIS	989	5.0%	34	3.3%	39	3.8%	367	4.6%	549	5.6%	
Comorbidity Index[a]												<.0001
	0	8194	41.5%	507	49.9%	491	48.2%	3530	44.6%	3666	37.4%	
	1	5832	29.5%	304	29.9%	286	28.1%	2469	31.2%	2773	28.3%	
	2+	5720	29.0%	206	20.3%	242	23.7%	1907	24.1%	3365	34.3%	
Predicted DS[b]												<.0001
	Good 0-2	17964	91.0%	992	97.5%	931	91.4%	7606	96.2%	8435	86.0%	
	Poor 3-4	1782	9.0%	25	2.5%	88	8.6%	300	3.8%	1369	14.0%	
Year of Diagnosis												
	2007	1465	7.4%	103	10.1%	82	8.0%	529	6.7%	751	7.7%	0.0002
	2008	2938	14.9%	161	15.8%	141	13.8%	1145	14.5%	1491	15.2%	
	2009	2976	15.1%	176	17.3%	147	14.4%	1169	14.8%	1484	15.1%	
	2010	2900	14.7%	139	13.7%	139	13.6%	1141	14.4%	1481	15.1%	
	2011	2835	14.4%	142	14.0%	138	13.5%	1166	14.7%	1389	14.2%	
	2012	3198	16.2%	132	13.0%	165	16.2%	1337	16.9%	1564	16.0%	
	2013	3434	17.4%	164	16.1%	207	20.3%	1419	17.9%	1644	16.8%	
Quarter of Year of Diagnosis												0.229
	Q1	4682	23.7%	233	22.9%	219	21.5%	1834	23.2%	2396	24.4%	
	Q2	4511	22.8%	219	21.5%	227	22.3%	1843	23.3%	2222	22.7%	
	Q3	5363	27.2%	283	27.8%	297	29.1%	2175	27.5%	2608	26.6%	
	Q4	5190	26.3%	282	27.7%	276	27.1%	2054	26.0%	2578	26.3%	
Cancer Stage												<.0001

	Stage IIIB	5499	27.8%	249	24.5%	236	23.2%	2390	30.2%	2624	26.8%	
	Stage IV	14247	72.2%	768	75.5%	783	76.8%	5516	69.8%	7180	73.2%	
Cancer Histology												<.0001
	Adenocarcinoma	10207	51.7%	664	65.3%	792	77.7%	3929	49.7%	4822	49.2%	
	Squamous	5241	26.5%	186	18.3%	90	8.8%	2252	28.5%	2713	27.7%	
	Large cell	499	2.5%	23	2.3%	13	1.3%	215	2.7%	248	2.5%	
	Others	3799	19.2%	144	14.2%	124	12.2%	1510	19.1%	2021	20.6%	
Radiation as First Course of Therapy		8116	41.1%	408	40.1%	347	34.1%	4011	50.7%	3350	34.2%	<.0001
Surgery as First Course of Therapy		1264	6.4%	31	3.0%	35	3.4%	560	7.1%	638	6.5%	<.0001
Receipt of Care from Hospital Affiliation with												
	NCI Designation	3195	16.2%	270	26.5%	234	23.0%	1572	19.9%	1119	11.4%	<.0001
	ECOG	4997	25.3%	297	29.2%	235	23.1%	2300	29.1%	2165	22.1%	<.0001
	Teaching Hospital	13134	66.5%	768	75.5%	727	71.3%	5570	70.5%	6069	61.9%	<.0001
	Major Affiliation with Medical School	7504	38.0%	473	46.5%	452	44.4%	3288	41.6%	3291	33.6%	<.0001

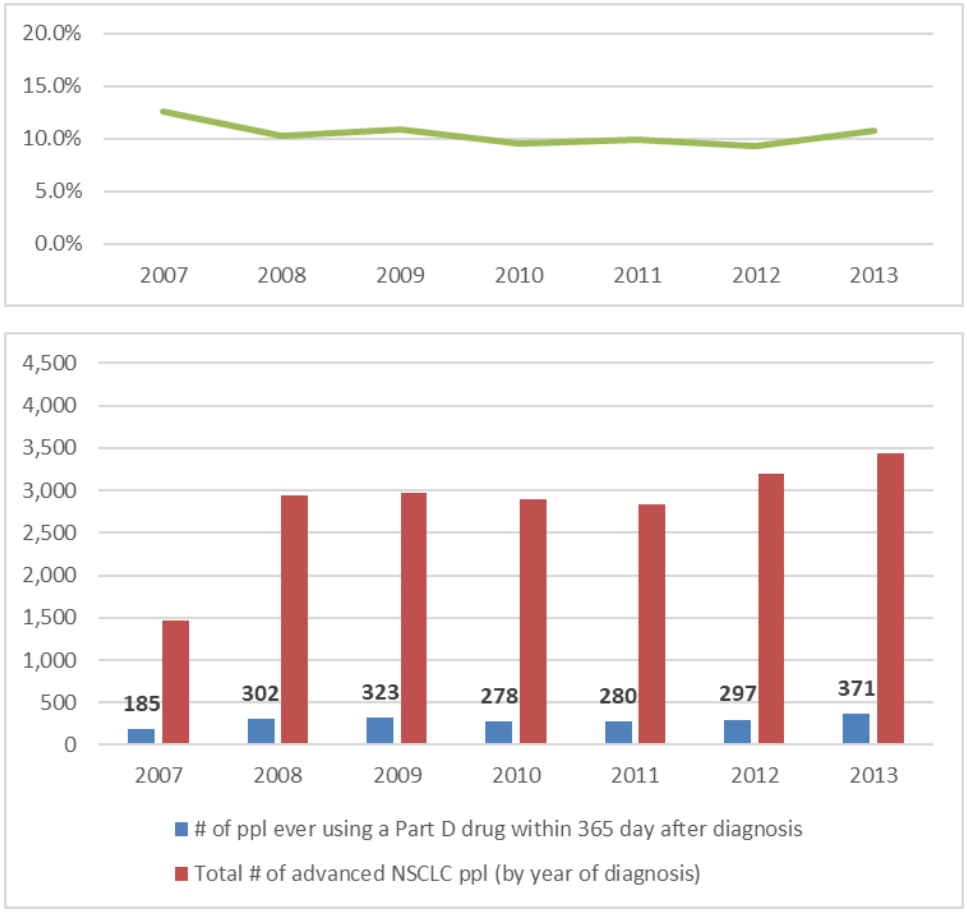
[a] Klabunde's adaptation of the Charlson comorbidity index[191] was used to assess cancer-specific Comorbidity Index with Charlson comorbidity index included comorbidities other than cancer.

[b] Predicted disability status (DS)[192] was calculated based on a validated claims-based algorithm developed by Davidoff AJ et al. This could serve as a proxy measure of performance status (PS), among older cancer population.

Abbreviation: 95% CI, 95% Confidence Interval; aRR: adjusted Relative risk; cRR: crude Relative Risk; DS, Disability Status; ECOG: the Eastern Cooperative Oncology Group; LIS: Low Income Subsidy; NSCLC: Non-Small Cell Lung Cancer.

During the observation period, about 10% of the advanced NSCLC population ever used a Part D drug within 12 months of diagnosis, including 1,019 patients using only Part D drugs and 1,017 patients using both Part B and Part D drugs within the period **(Figure 4.10A)**. Rates of Part D drug use decreased slightly over time, from 12.6% for patients diagnosed in 2007 to 10.8% for patients diagnosed in 2013. Specifically, 3 out of 5 Part D drugs approved during the study period were used as first Part D treatment by the patients **(Figure 4.10B)**, including erlotinib, crizotinib, and afatinib (gefitinib and ceritinib were not observed possible because of FDA announcement of restrictive use of geftinitb in previously treated patients and ceritinib's late approval in the study period). Of these, erlotinib accounted for more than 90% of all use.

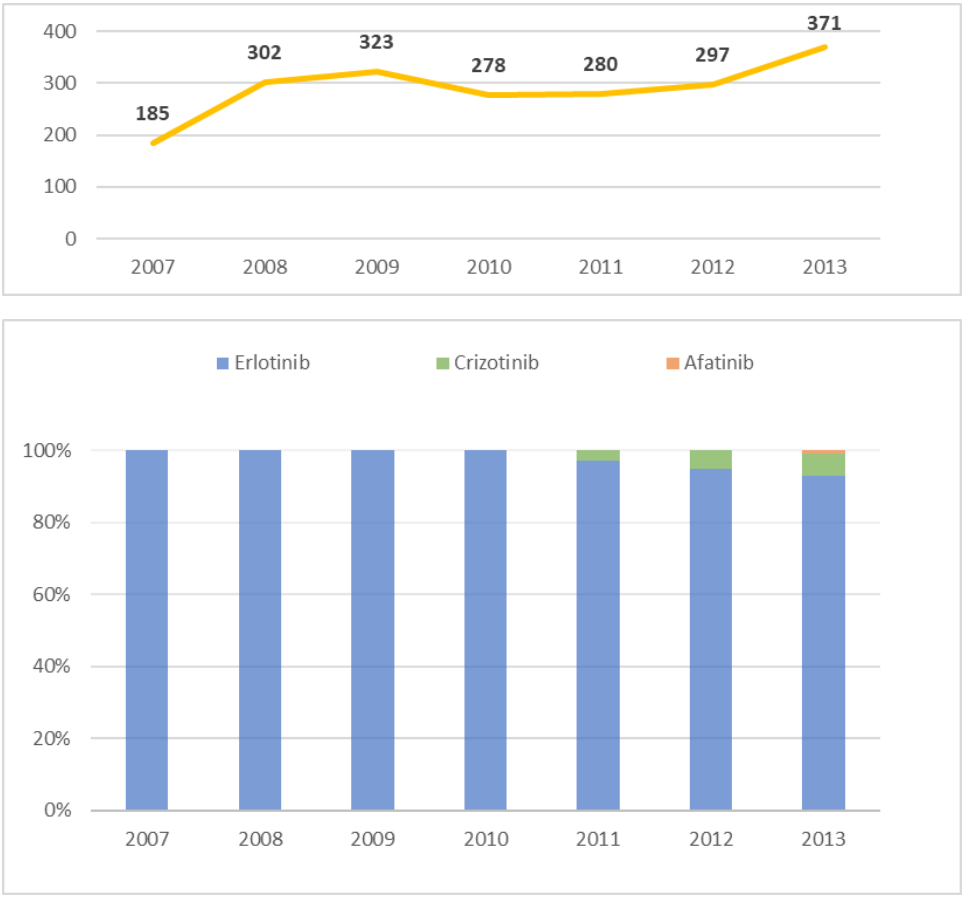
Figure 4.10A Utilization NSCLC Drugs on Medicare Part D within 12-month after Diagnosis of Advanced NSCLC, 2007-2014[a,b]



[a] The percentage of Part D drug users (green) was calculated as the number of people ever using a Part D drug within 365 days of advanced NSCLC diagnosis (blue) divided by the total number of advanced NSCLC patients of the year (red). Utilization is presented by patients' year of advanced NSCLC diagnosis.

[b] Among the ever Part D users, about 50% has used both Part B and Part D drugs during the 12 months of diagnosis. Please see **Appendix Figure 4.1A** for detailed composition on the utilization of Part D drugs.

Figure 4.10B First NSCLC Drugs on Medicare Part D within 12-month after Diagnosis of Advanced NSCLC, 2007-2014, by Drug Product[a]



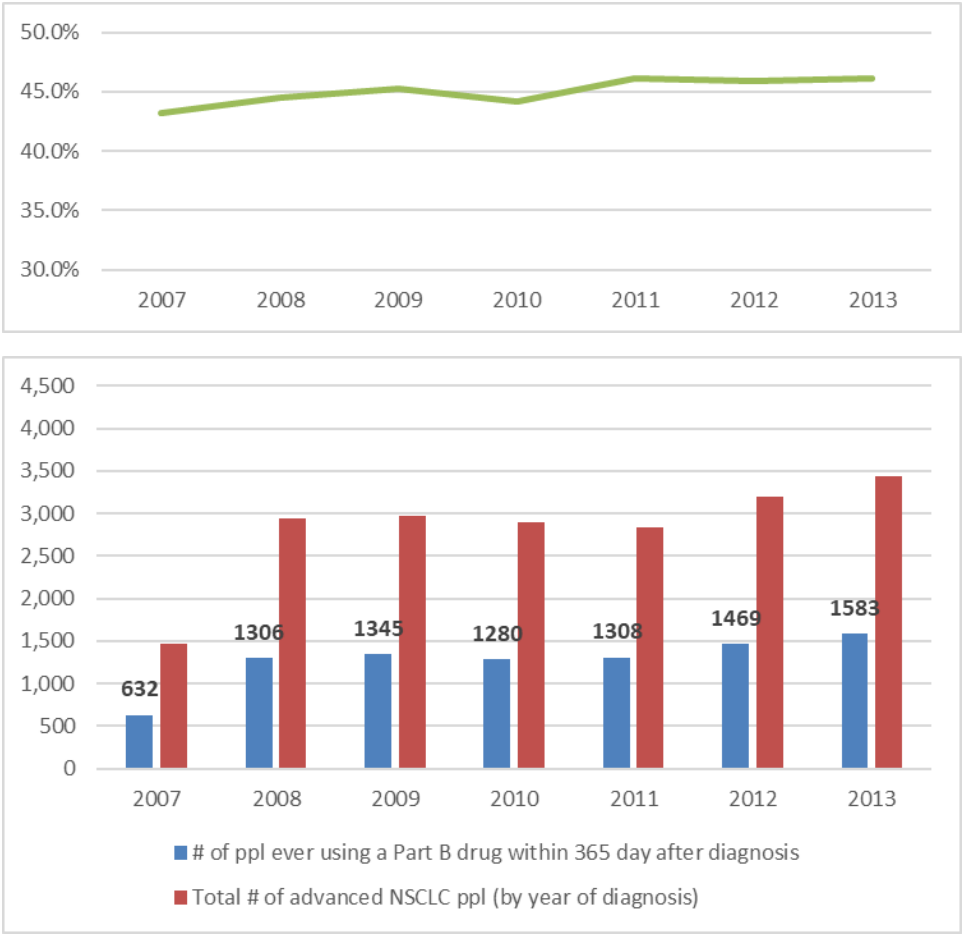
[a] The yellow line indicated the annual number of advanced NSCLC patients ever receiving Part D drug within 365 days of the diagnosis, presented by patients' year of advanced NSCLC diagnosis. Each bar of a year was composed of percentage of patients using specific Part D drug (represented by different color) within the year and summed to 100%. Drugs not shown were those not observed with any use by the patients during the study period.

On the other hand, the utilization of Part B drugs within 12-month of diagnosis was much higher than the utilization of Part D drugs, accounting for around 45% of the advanced NSCLC population, including 7,906 patients using only Part B drugs and 1,017 patients using both Part B and Part D drugs within the period. Overall, a slight increase was observed, from 43.1% for patients diagnosed in 2007 to 46.1% for patients diagnosed in 2013 **(Figure 4.11A)**.

Among the Part B drugs, platinum-based regimens consisting of all traditional chemotherapies were the most common first-line treatments. Specifically, carboplatin-based

regimens and cisplatin-based regimens accounted for 65-70% or 8-10% of all use over time, respectively **(Figure 4.11B)**. Regimens with targeted therapy (e.g., bevacizumab), however, accounted for only 10-14% of all use over the same period. Since ramucirumab was approved in the end of our study period, December 2014, there had not been any observation of ramucirumab use during the time.

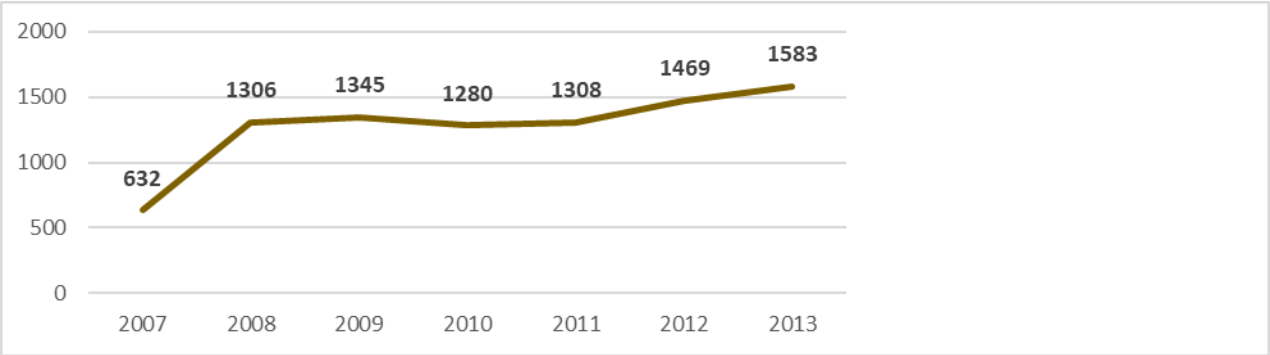
Figure 4.11A. Utilization of NSCLC Drugs on Medicare Part B within 12-month after Diagnosis of Advanced NSCLC, 2007-2014[a,b]

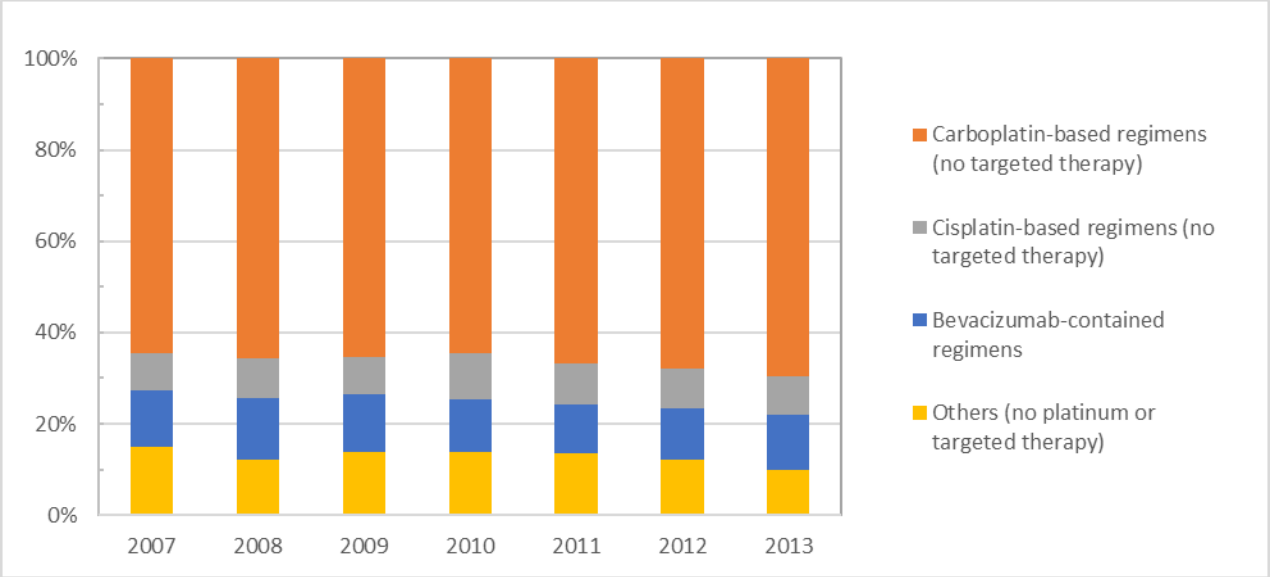


[a] The percentage of Part D drug users (green) was calculated as the number of people ever using a Part D drug within 365 days of advanced NSCLC diagnosis (blue) divided by the total number of advanced NSCLC patients of the year (red). Utilization is presented by patients' year of advanced NSCLC diagnosis. In addition, among the ever Part D users, about 50% has used both Part B and Part D drugs during the 12 months of diagnosis. Please see Appendix Figure 4.1A for detailed composition on the utilization of Part D drugs.

[b] Among mong the ever Part B users, more than 10% has used both Part B and Part D drugs during the 12 months of diagnosis. Please see **Appendix Figure 4.1B** for detailed composition on the utilization of Part D drugs.

Figure 4.11B. First NSCLC Drugs on Medicare Part B within 12-month after Diagnosis of Advanced NSCLC, 2007-2014, by Regimen[a]





[a] Utilization of Part B drugs were presented in terms of regimen rather than specific products because these drugs are mainly used in combination.
[a] The brown line indicated the annual number of advanced NSCLC patients ever receiving Part B drug within 365 days of the diagnosis, presented by patients' year of advanced NSCLC diagnosis. Each bar of a year was composed of percentage of patients using specific Part B regimen (represented by different color) within the year and summed to 100%.

A secondary goal for Aim 2 is to understand the factors associated with receipt of any Part D treatment (versus no Part D treatment). Characteristics of the cohort once categorized into this binary treatment assignment are provided in **Table 4.1B** below and difference between Part D treated and untreated patients are discussed below.

Table 4.1B Patient Characteristics at Baseline, Part D treated vs. No Part D treated (N=19,746)

	Grand Total N=19746		Part D drug use within 365 days N=2036		No Part D drug use within 365 days N=17710		
	N	%	N	%	N	%	p-value
Age							<.0001
65-69	4733	24.0%	444	21.8%	4289	24.2%	
70-74	5375	27.2%	473	23.2%	4902	27.7%	
75-79	4433	22.5%	461	22.6%	3972	22.4%	
80+	5205	26.4%	658	32.3%	4547	25.7%	
Sex							<.0001
Male	9745	49.4%	790	38.8%	8955	50.6%	
Female	10001	50.6%	1246	61.2%	8755	49.4%	
Race/Ethnicity							<.0001
Non-Hispanic White	14929	75.6%	1296	63.7%	13633	77.0%	
Non-Hispanic Black	2025	10.3%	135	6.6%	1890	10.7%	
Hispanic	1151	5.8%	137	6.7%	1014	5.7%	
Others	1641	8.3%	468	23.0%	1173	6.6%	
Marital Status							<.0001
Married	8903	45.1%	1056	51.9%	7847	44.3%	
Single	10092	51.1%	915	44.9%	9177	51.8%	
Unknown	751	3.8%	65	3.2%	686	3.9%	
Region							<.0001
North East	3765	19.1%	357	17.5%	3408	19.2%	
South	5746	29.1%	436	21.4%	5310	30.0%	
North Central	2571	13.0%	161	7.9%	2410	13.6%	
West	7664	38.8%	1082	53.1%	6582	37.2%	
Urban/Rural Residence							<.0001
Big Metro	10188	51.6%	1210	59.4%	8978	50.7%	
Metro	5694	28.8%	529	26.0%	5165	29.2%	
Urban	1227	6.2%	116	5.7%	1111	6.3%	
Less Urban	2125	10.8%	157	7.7%	1968	11.1%	
Rural	512	2.6%	24	1.2%	488	2.8%	
Census Tract % of without High School Degree							<.0001
00-05%	3114	15.8%	422	20.7%	2692	15.2%	
05-10%	4621	23.4%	471	23.1%	4150	23.4%	
10-20%	5953	30.1%	528	25.9%	5425	30.6%	
20-100%	6058	30.7%	615	30.2%	5443	30.7%	
Census Tract % below poverty							<.0001
00-05%	3303	16.7%	416	20.4%	2887	16.3%	
05-10%	4672	23.7%	511	25.1%	4161	23.5%	
10-20%	6109	30.9%	601	29.5%	5508	31.1%	

20-100%	5662	28.7%	508	25.0%	5154	29.1%	
Census Tract Household Median Income							<.0001
1st Quartile	4936	25.0%	407	20.0%	4529	25.6%	
2nd Quartile	4937	25.0%	444	21.8%	4493	25.4%	
3rd Quartile	4936	25.0%	513	25.2%	4423	25.0%	
4th Quartile	4937	25.0%	672	33.0%	4265	24.1%	
Receipt of Low Income Subsidy (LIS)							<.0001
Full LIS	6979	35.3%	796	39.1%	6183	34.9%	
No LIS	11778	59.6%	1167	57.3%	10611	59.9%	
Partial LIS	989	5.0%	73	3.6%	916	5.2%	
Comorbidity Index[a]							<.0001
0	8194	41.5%	998	49.0%	7196	40.6%	
1	5832	29.5%	590	29.0%	5242	29.6%	
2+	5720	29.0%	448	22.0%	5272	29.8%	
Predicted DS[b]							<.0001
Good 0-2	17964	91.0%	1923	94.4%	16041	90.6%	
Poor 3-4	1782	9.0%	113	5.6%	1669	9.4%	
Year of Diagnosis							
2007	1465	7.4%	185	9.1%	1280	7.2%	0.0127
2008	2938	14.9%	302	14.8%	2636	14.9%	
2009	2976	15.1%	323	15.9%	2653	15.0%	
2010	2900	14.7%	278	13.7%	2622	14.8%	
2011	2835	14.4%	280	13.8%	2555	14.4%	
2012	3198	16.2%	297	14.6%	2901	16.4%	
2013	3434	17.4%	371	18.2%	3063	17.3%	
Quarter of Year of Diagnosis							0.1314
Q1	4682	23.7%	452	22.2%	4230	23.9%	
Q2	4511	22.8%	446	21.9%	4065	23.0%	
Q3	5363	27.2%	580	28.5%	4783	27.0%	
Q4	5190	26.3%	558	27.4%	4632	26.2%	
Cancer Stage							<.0001
Stage IIIB	5499	27.8%	485	23.8%	5014	28.3%	
Stage IV	14247	72.2%	1551	76.2%	12696	71.7%	
Cancer Histology							<.0001
Adenocarcinoma	10207	51.7%	1456	71.5%	8751	49.4%	
Squamous	5241	26.5%	276	13.6%	4965	28.0%	
Large cell	499	2.5%	36	1.8%	463	2.6%	
Others	3799	19.2%	268	13.2%	3531	19.9%	
Radiation as First Course of Therapy	8116	41.1%	755	37.1%	7361	41.6%	<.0001
Surgery as First Course of Therapy	1264	6.4%	66	3.2%	1198	6.8%	<.0001
Receipt of Care from Hospital Affiliation with							
NCI Designation	3195	16.2%	504	24.8%	2691	15.2%	<.0001
ECOG	4997	25.3%	532	26.1%	4465	25.2%	0.3669
Teaching Hospital	13134	66.5%	1495	73.4%	11639	65.7%	<.0001
Major Affiliation with Medical School	7504	38.0%	925	45.4%	6579	37.1%	<.0001

[a] Klabunde's adaptation of the Charlson comorbidity index[191] was used to assess cancer-specific Comorbidity Index with Charlson comorbidity index included comorbidities other than cancer.

[b] Predicted disability status (DS)[192] was calculated based on a validated claims-based algorithm developed by Davidoff AJ et al. This could serve as a proxy measure of performance status (PS), among older cancer population.

Abbreviation: 95% CI, 95% Confidence Interval; aRR: adjusted Relative risk; cRR: crude Relative Risk; DS, Disability Status; ECOG: the Eastern Cooperative Oncology Group; LIS: Low Income Subsidy; NSCLC: Non-Small Cell Lung Cancer.

Overall, among the advanced NSCLC population, 10.3% ever received a Part D drug treatment within the year of diagnosis and 89.7% did not **(Table 4.1B)**. When comparing those who received a Part D drug treatment to those who did not, Part D drug users were older (Age 75+: 54.9% vs. 48.1%, $p<0.0001$), had a higher proportion of female users (61.2% vs. 49.4%, $p<0.0001$), and were more likely to be married (51.9% vs. 41.3%, $p<0.0001$). In addition, users consisted of a much higher proportion of "Other" racial groups, which includes Asian, than non-users, 23.0% vs 6.6%, respectively ($p<0.0001$).

In terms of socioeconomic status, patients who received Part D drug treatments had higher education measured at the census tract level (56.1% vs. 61.3% living in areas with ≥10% residents with no High School Degree, $p<0.0001$) and higher household income at census tract level (residents with income above the 4th quartile, $73,391: 33.0% vs. 24.1%, $p<0.0001$). Although more than one third of both groups received full low-income subsidies (LIS) to offset out-of-pocket costs for drugs obtained through Medicare Part D, more Part D drug users received full cost-sharing assistance within the year of diagnosis (39.1% vs. 34.9%).

Health status measured through either comorbidity or disability scores was generally better among Part D drug users than that among non-users (comorbidity 0-1: 78.0% vs. 70.2%, $p<0.0001$; good predicted disability status: 94.4% vs. 90.6%, $p<0.0001$) although more patients who used Part D drugs were diagnosed with stage IV cancers as compared with non-users (76.2% vs. 71.7%, $p<0.0001$). Adenocarcinoma accounts for the largest proportion among both groups (71.5% and 49.4% of tumor types, respectively), particularly among those receiving Part D drug treatments within the year of diagnosis. Among all adenocarcinomas, 14% ever received Part D drugs within the year of diagnosis.

In model examinations to further consider factors associated with filling Part D drug prescriptions **(Table 4.2)**, we first compared patients ever using Part D drugs within the year of diagnosis with those never using any Part D drugs within the year of diagnosis. We found that patients aged over 80 years at diagnosis (adjusted Risk Ratio (aRR): 1.35 [95% CI: 1.19-1.50], female (aRR: 1.53 [95% CI: 1.40-1.66], and married (aRR: 1.30 [95% CI: 1.19-1.43] were significantly more likely to receive Part D drug treatments in the 12-month post-diagnosis period. Race/ethnicity were also important factors in use of Part D treatments. Especially for the "Other" group, which includes Asian, the probability of using Part D treatments was more than 2 times that of non-Hispanic Whites (aRR: 2.26 [95% CI: 2.00-2.53].

Socioeconomic status was generally not associated with the use of Part D drug treatment after adjustment for other characteristics. In the bivariate analysis, we found that patients residing in census tract areas with lower education status (aRR from 0.65 to 0.75), greater poverty level (aRR from 0.71 to 0.87), or lower income (aRR from 0.61 to 0.76) were less likely receive Part D drug treatments. However, the effects were no longer significant when considering the effects of other factors in the multivariate examinations. For low income subsidies (LIS), on the other hand, in bivariate analysis patients who did not receive a full LIS were significantly less likely to receive Part D treatments, particularly among those with partial LIS (crude Risk Ratio ($cRR)_{\text{partial LIS}}$: 0.65 [95% CI:0.51-0.81]; $cRR_{\text{no LIS}}$: 0.87 [95% CI:0.79-0.94]). After adjustment for other clinical and socio-demographic factors, this association was attenuated ($aRR_{\text{partial LIS}}$: 0.83 [95% CI: 0.65-1.03;] $aRR_{\text{no LIS}}$: 0.81 [95% CI: 0.81-1.00]).

In terms of tumor characteristics, stage IV cancers (compared to stage IIIB cancers) or adenocarcinoma subtype (compared to other cancer histology) were associated with 26-82% higher probability of Part D treatment use. Patients with poor predicted disability status or higher

comorbidity burden were less likely to receive Part D treatments ($aRR_{poor\ DS}$: 0.67 [95% CI: 0.55-0.79]; $aRR_{CCI(2+)}$: 0.83 [95% CI: 0.74-0.92]). Having surgery or radiation as part of first course of therapy was associated with lower possibility of Part D drug use ($aRR_{surgery}$: 0.32 [95% CI: 0.24-0.40]; $aRR_{radiation}$: 0.88 [95% CI: 0.81-0.96]). Hospital affiliation was also significantly related to the use of Part D drug treatments; except NCI designation, patients ever receiving care from hospitals affiliated with the Eastern Cooperative Oncology Group (ECOG), a teaching hospital, or a medical school remain 12-25% more likely to receive Part D drug treatments after adjustment as compared to those never receiving care from these hospitals.

Table 4.2A Association between Key Factors and Part D Drug Treatment Use for Advanced Non-Small Cell Lung Cancer, among All Patients. (N=19,746)[a]

		cRR[a]	95% CI	aRR[a]	95% CI
Demographic Characteristics					
Age					
	65-69	Reference		Reference	
	70-74	0.94	(0.82, 1.06)	0.95	(0.84, 1.06)
	75-79	1.11	(0.97, 1.25)	1.10	(0.97, 1.23)
	80+	1.35	(1.20, 1.50)	1.34	(1.19, 1.50)
Sex					
	Male	Reference		Reference	
	Female	1.54	(1.41, 1.67)	1.53	(1.40, 1.66)
Race/Ethnicity					
	Non-Hispanic White	Reference		Reference	
	Non-Hispanic Black	0.77	(0.64, 0.91)	0.90	(0.74, 1.07)
	Hispanic	1.37	(1.16, 1.61)	1.24	(1.04, 1.47)
	Others	3.29	(2.99, 3.60)	2.26	(2.00, 2.53)
Marital Status					
	Married	Reference		Reference	
	Single	0.76	(0.70, 0.83)	0.77	(0.70, 0.84)
Geographic Characteristics					
Region					
	North East	Reference		Reference	
	South	0.80	(0.70, 0.91)	1.21	(1.04, 1.41)
	North Central	0.66	(0.55, 0.79)	0.75	(0.62, 0.89)
	West	1.49	(1.32, 1.66)	1.34	(1.17, 1.52)
Urban/Rural Residence					
	Big Metro	Reference		Reference	
	Metro	0.78	(0.71, 0.86)	0.95	(0.86, 1.05)
	Urban	0.80	(0.66, 0.95)	1.14	(0.94, 1.36)
	Less Urban	0.62	(0.53, 0.72)	1.02	(0.85, 1.21)
	Rural	0.39	(0.26, 0.58)	0.68	(0.44, 1.01)
Socioeconomic Status					
Census Tract % of Non-High School Degree					

00-05%	Reference		Reference	
05-10%	0.75	(0.66, 0.85)	0.85	(0.75, 0.96)
10-20%	0.65	(0.58, 0.73)	0.84	(0.72, 0.96)
20-100%	0.75	(0.66, 0.84)	0.94	(0.79, 1.10)
Census Tract % below poverty				
00-05%	Reference		Reference	
05-10%	0.87	(0.76, 0.98)	0.95	(0.83, 1.07)
10-20%	0.78	(0.69, 0.87)	0.96	(0.82, 1.11)
20-100%	0.71	(0.63, 0.80)	1.00	(0.81, 1.21)
Census Tract Household Median Income				
4th Quartile	Reference		Reference	
3rd Quartile	0.76	(0.69, 0.85)	0.95	(0.84, 1.07)
2nd Quartile	0.66	(0.59, 0.74)	0.93	(0.79, 1.09)
1st Quartile	0.61	(0.54, 0.68)	0.87	(0.71, 1.06)
Cost-Sharing Support Status				
Receipt of Low Income Subsidy (LIS)				
Full LIS	Reference		Reference	
No LIS	0.87	(0.79, 0.94)	0.90	(0.81, 1.00)
Partial LIS	0.65	(0.51, 0.81)	0.83	(0.65, 1.03)
Health Status				
Klabunde adapted Comorbidity Index[b]				
0	Reference		Reference	
1	0.83	(0.75, 0.91)	0.94	(0.85, 1.02)
2+	0.64	(0.57, 0.71)	0.83	(0.74, 0.92)
Predicted DS[c]				
Good 0-2	Reference		Reference	
Poor 3-4	0.59	(0.49, 0.71)	0.67	(0.55, 0.79)
Tumor-Related Characteristics				
Year of Diagnosis				
2007	Reference		Reference	
2008	0.81	(0.68, 0.96)	0.82	(0.68, 0.97)
2009	0.86	(0.72, 1.01)	0.86	(0.72, 1.02)
2010	0.76	(0.63, 0.90)	0.76	(0.63, 0.90)
2011	0.78	(0.65, 0.93)	0.75	(0.63, 0.89)
2012	0.74	(0.61, 0.87)	0.72	(0.60, 0.86)
2013	0.86	(0.72, 1.00)	0.87	(0.73, 1.02)
Quarter of Year of Diagnosis				
Q1	Reference		Reference	
Q2	1.02	(0.90, 1.15)	1.00	(0.88, 1.12)
Q3	1.12	(0.99, 1.25)	1.06	(0.94, 1.18)
Q4	1.11	(0.99, 1.25)	1.06	(0.94, 1.18)
Cancer Stage				
Stage IIIB	Reference		Reference	
Stage IV	1.23	(1.12, 1.36)	1.26	(1.14, 1.39)
Cancer Histology				
Adenocarcinoma	2.35	(2.13, 2.57)	1.82	(1.61, 2.06)
Squamous	0.43	(0.38, 0.49)	0.88	(0.74, 1.03)
Large Cell	0.69	(0.50, 0.95)	1.15	(0.82, 1.60)
Radiation as First Course of Therapy				
No	Reference		Reference	
Yes	0.83	(0.76, 0.90)	0.88	(0.81, 0.96)
Surgery as First Course of Therapy				
No	Reference		Reference	
Yes	0.49	(0.38, 0.62)	0.32	(0.24, 0.40)
Institutional Affiliation				

Receipt of Care from Hospital Affiliation with				
NCI Designation	1.70	(1.55, 1.87)	1.08	(0.96, 1.20)
ECOG	1.04	(0.95, 1.14)	1.12	(1.01, 1.24)
Teaching Hospital	1.39	(1.26, 1.52)	1.25	(1.12, 1.39)
Major Affiliation with Medical School	1.36	(1.25, 1.47)	1.14	(1.02, 1.26)

[a] Modified Poisson Regression[196] were applied to estimate the crude and adjusted effects of key sociodemographic, and health system factors. Bivariate analysis was used to evaluate the unadjusted effect of a single independent variable on the outcome. multivariate models were used to estimate adjusted while controlling for all key variables listed in the table.
[b] Klabunde's adaptation of the Charlson comorbidity index[191] was used to assess cancer-specific Comorbidity Index with Charlson comorbidity index included comorbidities other than cancer.
[c] Predicted disability status (DS)[192] was calculated based on a validated claims-based algorithm developed by Davidoff AJ et al. This could serve as a proxy measure of performance status (PS), among older cancer population.
Abbreviation: 95% CI, 95% Confidence Interval; aRR: adjusted Relative risk; cRR: crude Relative Risk; DS, Disability Status; ECOG: the Eastern Cooperative Oncology Group; LIS: Low Income Subsidy; NSCLC: Non-Small Cell Lung Cancer.

In another examination of key factors associated with Part D use, we excluded those did not receive any drug-based treatment within the year of diagnosis (i.e., restricting to treated population) **(Table 4.2B)** because the never-treated group differed from other treated groups, particularly in their health and socioeconomic status. Specifically, in this analysis, we compared patients using Part D drugs with those only using Part B drugs within the year of diagnosis.

We found the results were consistent between models including and excluding patients who did not receive drug-based treatment. However, comorbidity and hospital affiliations were no longer statistically when excluding patients who did not receive treatment. Importantly, the association with receipt of Part D treatments in the 12 months since diagnosis became stronger among patients aged over 80 years at diagnosis (aRR: 1.91 [95% CI: 1.72-2.12]) and among LIS groups ($aRR_{\text{partial LIS}}$: 0.82 [95% CI: 0.66-1.00]; $aRR_{\text{no LIS}}$: 0.78 [95% CI: 0.71-0.86]) in models that excluded untreated patients. One thing worth noting was the predicted disability status; the direction of association appeared to change. In other words, among treated population, patients with poor predicted disability status appeared to be more likely to receive Part D treatment for the advanced NSCLC. However, the effect became not significant after controlling other factors (aRR: 1.10 [95% CI: 0.95-1.27]).

Table 4.2B Association between Key Factors and Part D Drug Treatment Use for Advanced Non-Small Cell Lung Cancer, among Drug Treated Patients. (N=9,942)[a]

	cRR[a]	95% CI	aRR[a]	95% CI
Demographic Characteristics				
Age				
65-69	Reference		Reference	
70-74	1.00	(0.89, 1.13)	0.98	(0.87, 1.09)
75-79	1.11	(1.18, 1.50)	1.24	(1.11, 1.39)
80+	2.32	(2.09, 2.57)	1.91	(1.72, 2.12)
Sex				
Male	Reference		Reference	
Female	1.57	(1.44, 1.70)	1.46	(1.35, 1.59)
Race/Ethnicity				
Non-Hispanic White	Reference		Reference	
Non-Hispanic Black	0.95	(0.81, 1.12)	0.97	(0.74, 1.07)
Hispanic	1.48	(1.27, 1.73)	1.22	(1.04, 1.47)
Others	3.02	(2.79, 3.28)	1.95	(1.75, 2.16)
Marital Status				
Married	Reference		Reference	
Single	1.04	(0.96, 1.12)	0.92	(0.85, 1.00)
Geographic Characteristics				
Region				
North East	Reference		Reference	
South	0.86	(0.75, 0.97)	1.19	(1.03, 1.37)
North Central	0.70	(0.59, 0.83)	0.83	(0.70, 0.98)
West	1.51	(1.36, 1.68)	1.30	(1.15, 1.47)
Urban/Rural Residence				
Big Metro	Reference		Reference	
Metro	0.81	(0.74, 0.89)	0.99	(0.91, 1.08)
Urban	0.78	(0.66, 0.93)	1.06	(0.89, 1.26)
Less Urban	0.66	(0.57, 0.77)	1.06	(0.90, 1.25)
Rural	0.40	(0.27, 0.56)	0.65	(0.44, 0.96)
Socioeconomic Status				
Census Tract % of Non-High School Degree				
00-05%	Reference		Reference	
05-10%	0.80	(0.71, 0.90)	0.86	(0.77, 0.97)
10-20%	0.76	(0.68, 0.85)	0.84	(0.74, 0.96)
20-100%	0.91	(0.81, 1.01)	0.90	(0.77, 1.04)
Census Tract % below poverty				
00-05%	Reference		Reference	
05-10%	0.94	(0.84, 1.05)	0.97	(0.87, 1.09)
10-20%	0.90	(0.80, 1.00)	0.98	(0.85, 1.21)
20-100%	0.90	(0.81, 1.01)	0.97	(0.81, 1.16)
Census Tract Household Median Income				
4th Quartile	Reference		Reference	
3rd Quartile	0.84	(0.76, 0.93)	0.98	(0.87, 1.10)
2nd Quartile	0.75	(0.68, 0.84)	0.97	(0.84, 1.13)
1st Quartile	0.79	(0.70, 0.88)	1.01	(0.83, 1.21)
Cost-Sharing Support Status				
Receipt of Low Income Subsidy (LIS)				
Full LIS	Reference		Reference	
No LIS	0.65	(0.60, 0.70)	0.78	(0.71, 0.86)
Partial LIS	0.61	(0.49, 0.75)	0.82	(0.66, 1.00)

Health Status				
Klabunde adapted Comorbidity Index[b]				
0	Reference		Reference	
1	0.88	(0.80, 0.96)	0.94	(0.86, 1.02)
2+	0.86	(0.78, 0.95)	0.92	(0.84, 1.02)
Predicted DS[c]				
Good 0-2	Reference		Reference	
Poor 3-4	1.36	(1.15, 1.59)	1.10	(0.95, 1.27)
Tumor-Related Characteristics				
Year of Diagnosis				
2007	Reference		Reference	
2008	0.81	(0.69, 0.94)	0.84	(0.72, 0.98)
2009	0.84	(0.71, 0.98)	0.82	(0.70, 0.95)
2010	0.76	(0.64, 0.89)	0.73	(0.62, 0.86)
2011	0.75	(0.64, 0.88)	0.70	(0.60, 0.82)
2012	0.70	(0.60, 0.82)	0.65	(0.56, 0.76)
2013	0.80	(0.69, 0.93)	0.75	(0.64, 0.87)
Quarter of Year of Diagnosis				
Q1	Reference		Reference	
Q2	0.99	(0.88, 1.11)	0.97	(0.87, 1.08)
Q3	1.06	(0.95, 1.19)	0.99	(0.90, 1.10)
Q4	1.08	(0.97, 1.21)	1.02	(0.92, 1.13)
Cancer Stage				
Stage IIIB	Reference		Reference	
Stage IV	1.30	(1.19, 1.43)	1.23	(1.14, 1.35)
Cancer Histology				
Adenocarcinoma	2.12	(1.95, 2.32)	1.69	(1.50, 1.90)
Squamous	0.46	(0.41, 0.52)	0.86	(0.74, 1.01)
Large Cell	0.69	(0.51, 0.94)	1.07	(0.79, 1.46)
Radiation as First Course of Therapy				
No	Reference		Reference	
Yes	0.63	(0.58, 0.68)	0.79	(0.73, 0.85)
Surgery as First Course of Therapy				
No	Reference		Reference	
Yes	0.50	(0.40, 0.63)	0.51	(0.41, 0.65)
Institutional Affiliation				
Receipt of Care from Hospital Affiliation with				
NCI Designation	1.25	(1.14, 1.36)	1.03	(0.93, 1.14)
ECOG	0.89	(0.81, 0.97)	1.03	(0.93, 1.13)
Teaching Hospital	1.12	(1.03, 1.23)	1.09	(0.99, 1.20)
Major Affiliation with Medical School	1.13	(1.05, 1.22)	1.14	(1.04, 1.26)

[a] Modified Poisson Regression[196] were applied to estimate the crude and adjusted effects of key sociodemographic, and health system factors. Bivariate analysis was used to evaluate the unadjusted effect of a single independent variable on the outcome. multivariate models were used to estimate adjusted while controlling for all key variables listed in the table.

[b] Klabunde's adaptation of the Charlson comorbidity index[191] was used to assess cancer-specific Comorbidity Index with Charlson comorbidity index included comorbidities other than cancer.

[c] Predicted disability status (DS)[192] was calculated based on a validated claims-based algorithm developed by Davidoff AJ et al. This could serve as a proxy measure of performance status (PS), among older cancer population.

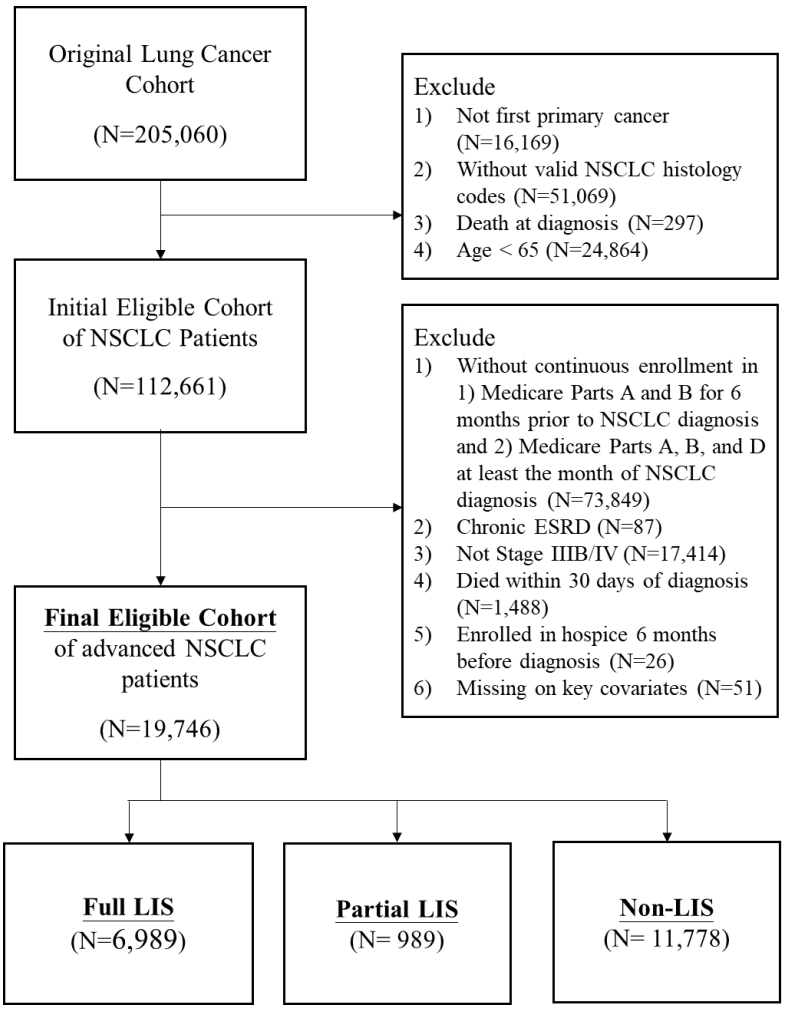
Abbreviation: 95% CI, 95% Confidence Interval; aRR: adjusted Relative risk; cRR: crude Relative Risk; DS, Disability Status; ECOG: the Eastern Cooperative Oncology Group; LIS: Low Income Subsidy; NSCLC: Non-Small Cell Lung Cancer.

4.3 AIM 3 – Evaluate the effect of low-income subsidies for Medicare Part D medications on treatment initiation among patients with advanced non-small cell lung cancer (NSCLC) from 2007 to 2014.

In this aim, we hypothesized that: 1) for medications covered under Part D, due to the higher cost-sharing required for patients who do not receive low income subsidies, time to initiation is shorter among patients with (full or partial) low-income subsidies as compared to those without; 2) for medications covered under Part B, due to the availability of supplemental insurance coverage for reducing or eliminating out-of-pocket costs for most Medicare enrollees, there is no difference in the time to initiation among patients with low-income subsidies as compared to those without.

Derived from the final eligible cohort of advanced NSCLC patients from Aim 2 (N=19,746), we further grouped the patients into three subsidy groups based on their low-income subsidy status at time of diagnosis. As a result, we identified 6,989 patients with Full subsidy, 11,778 with no subsidy, and 989 with partial subsidy **(Figure 4.12)**.

Figure 4.12 Flow chart of the study population selection



Abbreviation: ESRD, end-stage renal disease; LIS, low-income subsidy; NSCLC, non-small cell lung cancer.

In the examination of patient baseline characteristics **(Table 4.3, Pre-IPTW)** we found that patients without any LIS (i.e., non-LIS) were older than those with partial or full LIS (aged 80 or over: 23.1% for full LIS vs. 28.7% for non-LIS vs. 21.1% for partial LIS, p<0.0001) Compared to those with full subsidy, patients without full subsidy (i.e., non-LIS or partial LIS) consisted of more women (49.4% for full LIS vs. 51.4% for non-LIS vs. 50.4% for partial LIS, p<0.0001) and Non-Hispanic Whites (52.7% for full LIS vs. 89.4% for non-LIS vs. 73.2% for partial LIS, p<0.0001). Most of the population lived in the West or South regions (79.5% for full

LIS vs. 61.1% for non-LIS vs. 67.0% for partial LIS, p<0.0001) and Big Metro/Metro areas (80.4% for full LIS vs. 81.1% for non-LIS vs. 73.2% for partial LIS, p<0.0001). In terms of socioeconomic status, patients with any subsidy (i.e., full or partial LIS groups) were more likely to live in an area with lower median incomes (Census Tract Household Median Income at first two quartiles: 65.7% for full LIS, 73.4% for partial LIS vs. 39.6% for non-LIS, p<0.0001) and with lower education level at Census Tract level (Census Tract of more than 20% without high school degree: 50.1% for full LIS, 38.7% for partial LIS vs. 18.5% for non-LIS, p<0.0001), as compared to those without any subsidy. In terms of health status, more patients with full subsidy were in poorer status based on comorbidity index (2+: 35.6% for full LIS vs. 30.7% for partial LIS vs. 24.9% for non-LIS, p<0.0001) and predicted disability status (Poor 3-4: 17.1% for full LIS vs. 4.5% for non-LIS vs. 5.7% for partial LIS p<0.0001). Across groups, around 70% were diagnosed with stage IV cancers and around half had adenocarcinoma subtype.

Table 4.3 Baseline Patient Characteristics before and after Inverse Probability Treatment Weight (IPTW)

	Pre-IPTW							Post-IPTW[c]						
	Full LIS at diagnosis		Non-LIS at diagnosis		Partial LIS at diagnosis			Full LIS at diagnosis		Non-LIS at diagnosis		Partial LIS at diagnosis		
	6979		11778		989			6911		12046		948		
	N	%	N	%	N	%	p-value	N	%	N	%	N	%	p-value
Age							<.0001							0.2707
65-69	1855	26.6%	2583	21.9%	295	29.8%		1599	23.1%	2890	24.0%	240	25.3%	
70-74	1960	28.1%	3149	26.7%	266	26.9%		1878	27.2%	3355	27.9%	265	28.0%	
75-79	1552	22.2%	2662	22.6%	219	22.1%		1545	22.4%	2678	22.2%	209	22.0%	
80+	1612	23.1%	3384	28.7%	209	21.1%		1889	27.3%	3124	25.9%	234	24.7%	
Sex							0.0291							0.8979
Male	3531	50.6%	5723	48.6%	491	49.6%		3413	49.4%	5977	49.6%	464	48.9%	
Female	3448	49.4%	6055	51.4%	498	50.4%		3498	50.6%	6070	50.4%	484	51.1%	
Race/Ethnicity							<.0001							0.0035***
Non-Hispanic White	3677	52.7%	10528	89.4%	724	73.2%		5183	75.0%	8857	73.5%	705	74.4%	
Non-Hispanic Black	1339	19.2%	518	4.4%	168	17.0%		723	10.5%	1243	10.3%	91	9.6%	
Hispanic	795	11.4%	312	2.6%	44	4.4%		410	5.9%	683	5.7%	62	6.5%	
Others	1168	16.7%	420	3.6%	53	5.4%		595	8.6%	1264	10.5%	90	9.5%	
Marital Status							<.0001							0.5321
Married	2126	30.5%	6440	54.7%	337	34.1%		3019	43.7%	5193	43.1%	386	40.7%	
Single	4578	65.6%	4905	41.6%	609	61.6%		3625	52.5%	6393	53.1%	523	55.2%	
Unknown	275	3.9%	433	3.7%	43	4.3%		267	3.9%	461	3.8%	39	4.1%	
Region							<.0001							0.0007***
North East	821	11.8%	2763	23.5%	181	18.3%		1492	21.6%	2336	19.4%	169	17.8%	
South	2230	32.0%	3054	25.9%	462	46.7%		1947	28.2%	3369	28.0%	302	31.9%	
North Central	610	8.7%	1816	15.4%	145	14.7%		855	12.4%	1604	13.3%	121	12.8%	
West	3318	47.5%	4145	35.2%	201	20.3%		2618	37.9%	4737	39.3%	356	37.6%	
Urban/Rural Residence							<.0001							0.7708
Big Metro	3717	53.3%	6018	51.1%	453	45.8%		3439	49.8%	6119	50.8%	463	48.8%	
Metro	1889	27.1%	3534	30.0%	271	27.4%		2077	30.1%	3539	29.4%	284	30.0%	
Urban	387	5.5%	777	6.6%	63	6.4%		473	6.8%	781	6.5%	71	7.5%	
Less Urban	794	11.4%	1168	9.9%	163	16.5%		749	10.8%	1292	10.7%	101	10.7%	
Rural	192	2.8%	281	2.4%	39	3.9%		173	2.5%	315	2.6%	28	3.0%	
Census Tract % of Non-High School Degree							<.0001							0.4100
00-05%	454	6.5%	2579	21.9%	81	8.2%		1031	14.9%	1856	15.4%	122	12.9%	
05-10%	975	14.0%	3475	29.5%	171	17.3%		1655	23.9%	2792	23.2%	226	23.8%	
10-20%	2054	29.4%	3545	30.1%	354	35.8%		2099	30.4%	3665	30.4%	303	32.0%	
20-100%	3496	50.1%	2179	18.5%	383	38.7%		2126	30.8%	3734	31.0%	297	31.3%	
Census Tract % below poverty							<.0001							0.2980
00-05%	562	8.1%	2645	22.5%	96	9.7%		1186	17.2%	1968	16.3%	145	15.3%	
05-10%	1033	14.8%	3442	29.2%	197	19.9%		1586	22.9%	2833	23.5%	208	21.9%	
10-20%	2171	31.1%	3582	30.4%	356	36.0%		2152	31.1%	3789	31.5%	294	31.0%	
20-100%	3213	46.0%	2109	17.9%	340	34.4%		1988	28.8%	3456	28.7%	301	31.8%	
Census Tract Household Median Income							<.0001							0.2441
1st quartile	2791	40.0%	1811	15.4%	334	33.8%		1729	25.0%	3004	24.9%	254	26.8%	
2nd quartile	1793	25.7%	2851	24.2%	293	29.6%		1763	25.5%	3094	25.7%	254	26.8%	
3rd quartile	1393	20.0%	3322	28.2%	221	22.3%		1665	24.1%	2977	24.7%	237	25.0%	

4th quartile	1002	14.4%	3794	32.2%	141	14.3%		1755	25.4%	2971	24.7%	203	21.4%	
Comorbidity Index[a]							<.0001							0.5093
0	2470	35.4%	5320	45.2%	404	40.8%		2811	40.7%	4894	40.6%	397	41.9%	
1	2025	29.0%	3526	29.9%	281	28.4%		2022	29.3%	3538	29.4%	292	30.8%	
2+	2484	35.6%	2932	24.9%	304	30.7%		2079	30.1%	3614	30.0%	259	27.3%	
Predicted DS[b]							<.0001							0.6185
Good 0-2	5788	82.9%	11243	95.5%	933	94.3%		6280	90.9%	10929	90.7%	869	91.7%	
Poor 3-4	1191	17.1%	535	4.5%	56	5.7%		631	9.1%	1117	9.3%	79	8.3%	
Year of Diagnosis							<.0001							0.9829
2007	537	7.7%	837	7.1%	91	9.2%		487	7.0%	879	7.3%	69	7.3%	
2008	1048	15.0%	1711	14.5%	179	18.1%		994	14.4%	1772	14.7%	145	15.3%	
2009	1069	15.3%	1745	14.8%	162	16.4%		1033	14.9%	1843	15.3%	137	14.5%	
2010	1088	15.6%	1656	14.1%	156	15.8%		1019	14.7%	1760	14.6%	145	15.3%	
2011	1061	15.2%	1620	13.8%	154	15.6%		985	14.3%	1712	14.2%	141	14.9%	
2012	1089	15.6%	1974	16.8%	135	13.7%		1139	16.5%	1965	16.3%	155	16.4%	
2013	1087	15.6%	2235	19.0%	112	11.3%		1254	18.1%	2116	17.6%	156	16.5%	
Quarter of Year of Diagnosis							0.8197							0.8999
Q1	1644	23.6%	2793	23.7%	245	24.8%		1643	23.8%	2889	24.0%	236	24.9%	
Q2	1585	22.7%	2692	22.9%	234	23.7%		1576	22.8%	2716	22.5%	221	23.3%	
Q3	1933	27.7%	3175	27.0%	255	25.8%		1917	27.7%	3311	27.5%	243	25.6%	
Q4	1817	26.0%	3118	26.5%	255	25.8%		1776	25.7%	3130	26.0%	248	26.2%	
Cancer Stage							0.0063							0.2537
Stage IIIB	2033	29.1%	3182	27.0%	284	28.7%		1966	28.4%	3293	27.3%	266	28.1%	
Stage IV	4946	70.9%	8596	73.0%	705	71.3%		4945	71.6%	8754	72.7%	682	71.9%	
Cancer Histology														
Adenocarcinoma	3361	48.2%	6390	54.3%	456	46.1%	<.0001	3510	50.8%	6166	51.2%	487	51.4%	0.8533
Squamous	2100	30.1%	2840	24.1%	301	30.4%	<.0001	1843	26.7%	3206	26.6%	257	27.1%	0.9505
Large cell	170	2.4%	304	2.6%	25	2.5%	0.8290	174	2.5%	298	2.5%	24	2.5%	0.9788
Others	1348	19.3%	2244	19.1%	207	20.9%	0.3481	1384	20.0%	2377	19.7%	180	19.0%	0.7361
Radiation as First Course of Therapy	2534	36.3%	5168	43.9%	414	41.9%	<.0001	2898	41.9%	4953	41.1%	375	39.6%	0.4520
Surgery as First Course of Therapy	339	4.9%	871	7.4%	54	5.5%	<.0001	439	6.4%	762	6.3%	64	6.8%	0.6238
Receipt of Care from Hospital Affiliation with NCI Designation	910	13.0%	2173	18.4%	112	11.3%	<.0001	1205	17.4%	2035	16.9%	153	16.1%	0.4586
ECOG	1266	18.1%	3471	29.5%	260	26.3%	<.0001	1819	26.3%	3125	25.9%	215	22.7%	0.0571
Teaching Hospital	4441	63.6%	8052	68.4%	641	64.8%	<.0001	4617	66.8%	8076	67.0%	616	65.0%	0.4183
Major Affiliation with Medical School	2291	32.8%	4820	40.9%	393	39.7%	<.0001	2679	38.8%	4648	38.6%	350	36.9%	0.5390

[a] Klabunde's adaptation of the Charlson comorbidity index[191] was used to assess cancer-specific Comorbidity Index with Charlson comorbidity index included comorbidities other than cancer.

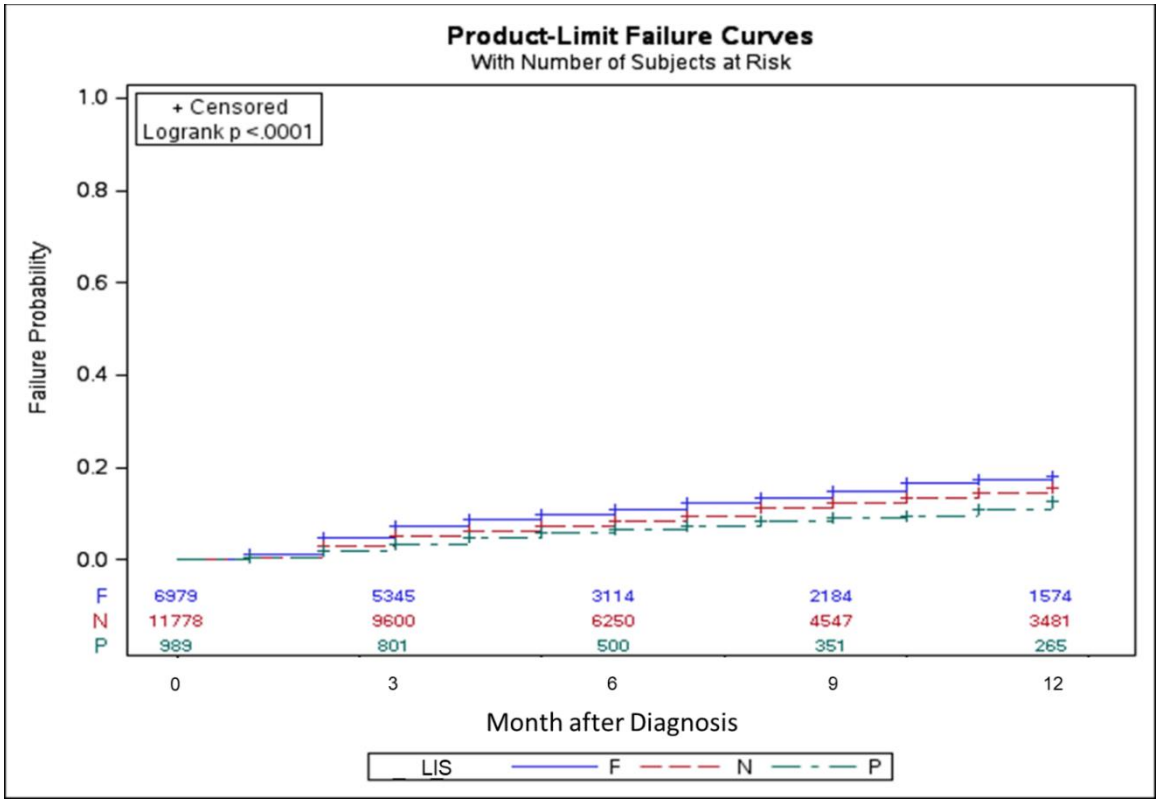
[b] Predicted disability status (DS)[192] was calculated based on a validated claims-based algorithm developed by Davidoff AJ et al. This could serve as a proxy measure of performance status (PS), among older cancer population.

[c] The standardized mean differences[197] post IPTW were all below 0.10 between groups (Non-LIS vs Full LIS; Partial LIS vs LIS), suggesting negligible imbalance in patient baseline characteristics between groups for the analysis. **(Appendix Table 4.5).**

Abbreviation: DS, Disability Status; ECOG: the Eastern Cooperative Oncology Group; LIS: Low Income Subsidy; NCI, the National Cancer Institute; NSCLC: Non-Small Cell Lung Cancer.

During the 12-month period after being diagnosed with advanced NSCLC, around 10% of patients initiated Part D treatments (11.4% for full LIS, 9.9% for non-LIS, 7.4% for partial LIS) **(Figure 4.13)**. The time to initiate Part D treatments was shorter among patients with full-LIS as compared to those with partial LIS or with no subsidy. The mean time from diagnosis to initiation of orally-administered targeted therapies was 10.8 (SD: 0.04) months for full LIS, 11.1 (SD: 0.03) months for non-LIS, and 11.3 (SD: 0.08) months for partial LIS, respectively ($p<0.0001$).

Figure 4.13 Product-Limit Failure[a] Curves for Time-to-Initiate Part D Treatments by Low-Income Subsidy (LIS) Status



[a] "Failure" indicates the outcome of interest, which is the initiation of Part D treatments.
Abbreviation: LIS, low-income subsidy; F as full LIS, N as non-LIS, and P as partial LIS.

Further in the examination through Cox models, we found that, as compared to patients with full subsidy, those without full subsidy (i.e., non-LIS, partial LIS) were less likely to initiate

Part D treatments, particularly among the partial LIS group **(Table 4.4)**. The effects remain even after controlling for other factors or applying IPTW to reduce the imbalance among groups (i.e., Non-LIS vs. Full LIS: $HR_{adjusted}$: 0.87 (95% CI: 0.78-0.98); HR_{IPTW}:0.87 (95% CI:0.79-0.95); Partial LIS vs. Full LIS: $HR_{adjusted}$: 0.80 (95% CI:0.63-1.02); HR_{IPTW}: 0.77 (95% CI:0.62-0.97)).

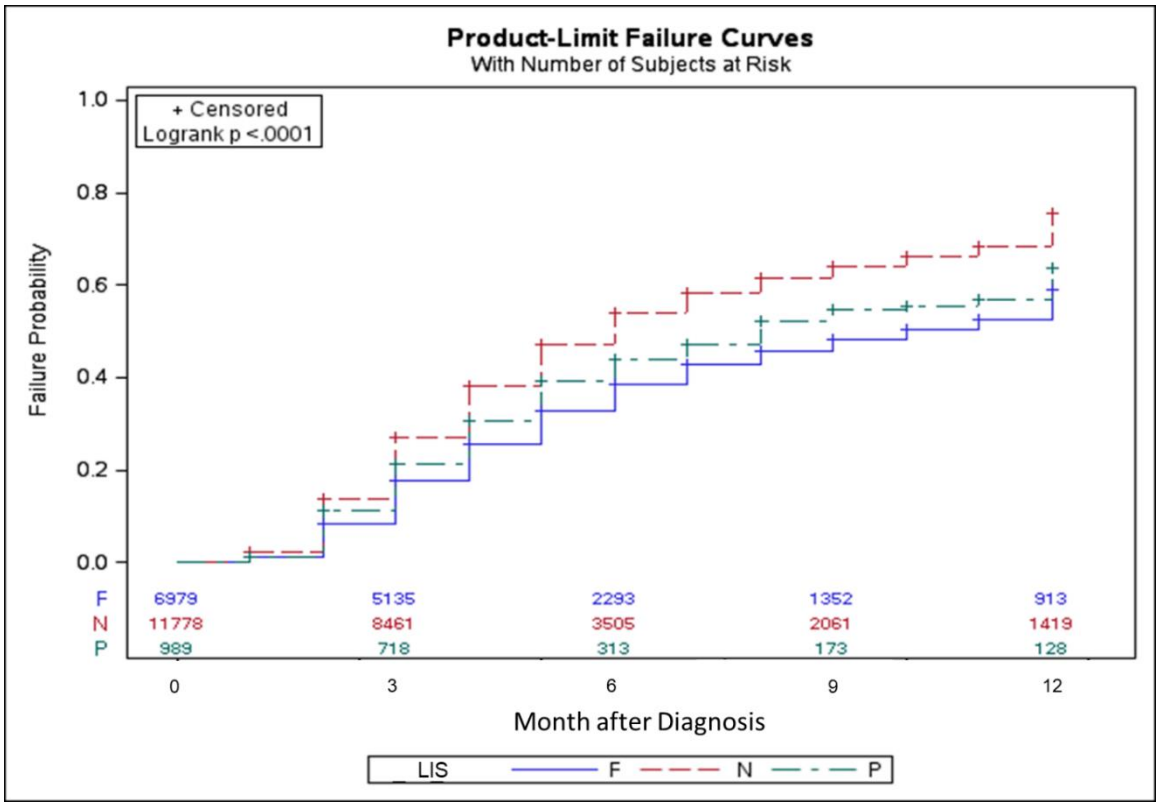
Table 4.4 Effect of Low-Income Subsidy on Time from Diagnosis to Initiation of Part D Treatments

	Model 1 No IPTW, Crude		**Model 2** No IPTW, Adjusted		**Model 3** IPTW weighted	
	HR	95% CI	HR	95% CI	HR	95% CI
Full LIS	1.00	Reference	1.00	Reference	1.00	Reference
Partial LIS	0.61	(0.48-0.77)	0.80	(0.63-1.02)	0.77	(0.62-0.97)
Non-LIS	0.79	(0.72-0.86)	0.87	(0.78-0.98)	0.87	(0.79-0.95)

Abbreviation: HR, hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weight; LIS, low-income subsidy.

Uptake of Part B drugs differed in important ways from what was observed for Part D drugs. As expected, Part B drugs were used more often by patients diagnosed with advanced NCSLC over our study period: 35.0% of patients initiated Part B treatment for full LIS, 51.6% for non-LIS, 40.6% for partial LIS during the 12-month period after being diagnosed with advanced NSCLC **(Figure 4.14)**. The time to initiate Part B treatments were shorter among the non-LIS group as compared to those with any subsidy (i.e., partial LIS or full LIS); the mean time to initiation was 7.0 (SD: 0.04) months for non-LIS, 7.9 (SD: 0.15) months for partial LIS, and 8.4 (SD: 0.06) months for full LIS, respectively ($p<0.0001$).

Figure 4.14 Product-Limit Failure[a] Curves for Time-to-Initiate Part B Treatments by Low-Income Subsidy (LIS) Status



[a] "Failure" indicates the outcome of interest, which is the initiation of Part B treatments.
Abbreviation: LIS, low-income subsidy; F as full LIS, N as non-LIS, and P as partial LIS.

When considering covariate adjustment in the Cox model, we found that patients without any subsidy were more likely to initiate Part B treatments compared to those with full subsidy or partial subsidy (e.g., Non-LIS vs. Partial LIS: $HR_{adjusted}$: 1.34 (95% CI: 1.21-1.50); HR_{IPTW}: 1.34 (95% CI: 1.21-1.49); Non-LIS vs. Full LIS: $HR_{adjusted}$: 1.42 (95% CI: 1.34-1.50); HR_{IPTW}: 1.41 (95% CI: 1.35-1.48)) **(Table 4.5)**. There was no difference in the Part B drug use between Partial LIS and Full LIS groups (Partial LIS vs. Full LIS: $HR_{adjusted}$: 1.05 (95% CI: 0.95-1.17); HR_{IPTW}: 1.05 (95% CI: 0.94-1.17)).

Table 4.5 Effect of Low-Income Subsidy on Time from Diagnosis to Initiation of Part B Treatments

	Model 1 No IPTW, Crude		**Model 2** No IPTW, Adjusted		**Model 3** IPTW weighted	
	HR	95% CI	HR	95% CI	HR	95% CI
Full LIS	1.00	Reference	1.00	Reference	1.00	Reference
Partial LIS	1.18	(1.06-1.31)	1.05	(0.95-1.17)	1.05	(0.94-1.17)
Non-LIS	1.55	(1.48-1.63)	1.42	(1.34-1.50)	1.41	(1.35-1.48)

Abbreviation: HR, hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weight; LIS, low-income subsidy.

CHAPTER FIVE: DISCUSSION

5.1 AIM 1

In Aim 1, we examined the changes in drug-specific prices for Part D medications approved for advanced NSCLC. We found higher entry prices at FDA approval in Part D advanced NSCLC drugs while older drugs also experienced considerable price hike by more than 45% from approval. In addition, drug prices remained high even when new drugs were approved to provide more treatment options for advanced NSCLC.

Our findings are consistent with the growing evidence on pricing of anticancer drugs in recent years.[198–201] An analysis of changes in reimbursements from the year of product launch for 18 orally administered anticancer drugs indicated a substantial increase in the monthly drug spending during the first year on the market; the mean spending ranged from $1,869 in 2000 to $11,325 in 2014.[198] In addition, most existing therapies have had substantial price increases since product launch.[198] In another examination on the trends in post-launch prices for orally administered anticancer drugs, Bennette et al also found that inflation-adjusted per patient monthly drug prices increased 5 percent each year between 2007 and 2013 after accounting for other factors related to price increases.[199] Our results point to this trend continuing. A separate study specifically focusing on targeted oral anticancer medications under Medicare even found an annually 12% increase in the mean drug prices.[200]

The study by Bennete et al suggested a general 10% increase in the price of oral anticancer drugs after supplemental US Food and Drug Administration approvals that expand the

patient population for treatment.[199] Our findings are lower, possibly because the subsequent approvals for the advanced NSCLC drugs in our study generally reduce the number of eligible patients rather than expand the drug indications. However, one drug is an exception, gefitinib. Gefitinib is the oldest tyrosine kinase inhibitor approved for advanced NSCLC. The use of gefitinib was restricted since 2005[194] due to its failure to show improved outcomes for patients with lung cancer in clinical studies and the drug company voluntarily withdrew the drug in the U.S. in 2011(effective in 2012).[195] The drug came back in 2015 with new evidence of its role in the treatment of a smaller but more specific patient population with EGFR mutations.[202] The price, in return, rose by almost 250%, from $2,296/month before withdrawal to $7,898/month in 2015, which is comparable to other EGFR-targeted agents at the time.

Notably, we observe minimal differences in the prices set for different dosage forms of the same drug covered under Part D. Drugs with lower doses priced at comparably high levels as the same drugs with higher doses. For example, there is less than $20 difference in the price between afatinib 20mg and 40mg in 2017, $7,684 and $7,699, respectively. An identical price, over $14,000/month, was even set for osimertinib in both 40mg and 80mg formulations since its approval.

These findings could suggest that current pricing strategies for novel oral advanced NSCLC drugs appears to follow the dominant price within the same therapeutic class. It is also possible that newer drugs are better than older agents and that the manufacturers set the drug prices according to the "value" the drugs could provide. However, in the context of Medicare Part D there are no current requirements that pricing reflect clinical benefit or other measures of "value." The definition of value of treatment varies across stakeholders. For example, for patients, the most important elements of treatment value might be effectiveness and side effects

at an individual level. For insurance plans, they could place more emphasis on effects at the population level. For manufactures, value may be product-specific profits and drug market share.

Our findings related to drug prices also reveal a lack of competitive pressure in the oral anticancer drug market. This might be contributed by the fact that cancer drugs are one of the six protected classes to cover under Medicare Part D (i.e., a Part D formulary should cover all or substantially all drugs in the protected therapeutic categories[24]), which aims to ensure patient access to their vital medications. By requiring all plans to offer anticancer medications, regardless of clinical benefit and cost, this may reduce plan negotiation power with manufacturers (and accordingly lower rebates / result in higher prices for these drugs[9]). The federal government is also prohibited from negotiating drug prices in the Part D program.[9] Given patent protection, orally-administered anticancer medications are expected to face limited price competition from generics.[10,71,203] Together, this leads to the high Part D cancer drug prices in the U.S. Further policy improvement to encourage the competitiveness of the marketplace, enhance price negotiation by governmental payers, and promote development of drug value assessment tools are necessary as part of the solution of high drug prices in cancer care.

We also examined formulary structure and the use of utilization management tools for Part D medications approved for advanced NSCLC. In this aspect, we found Part D coverage for advanced NSCLC drugs has improved in recent years; since 2015, almost all plans provide coverage for all advanced NSCLC drugs on the market. However, accessibility to available drug treatments remains a concern as utilization management tools were applied by most of the Part D plans and across treatment options (e.g., prior authorization and quantity limits). Further research to determine whether and how these utilization management tools affect patient timely access to drug treatment for advanced NSCLC is needed.

Although cancer drugs are one of the six protected classes in Medicare, we observed a lack of comprehensive coverage of all drugs during the first few years for our study period. This could be related to modifications of rules related to the treatment of the protected drug classes since the Part D programs went into effect, [24,204–206] possibly leading to fluctuations in benefit design. For example, in 2010 Congress made another modification to the so called "protected classes", seeking to review the existing six protected classes and to examine whether or not an exceptions process to the protected class rule was necessary. This could potentially increase the uncertainty in plan's decision in coverage for 2011. In addition, a coverage drop observed in 2011 could be the result of regulations issued by CMS, which intended to eliminate duplicative plan offerings and plans with low enrollment or from mergers among plan sponsors[207] or the withdrawal of gefitinib due to its failure in clinical trials and voluntary withdrawal by the drug company[195].

Concerns over affordability also continue due to the high use of percentage-based coinsurance as well as specialty / top tiering. In both cases, the patient's financial responsibility is a percentage of the point-of-sale drug price (around 33% in initial coverage phase, 25% in the coverage gap in 2019 with the Bipartisan Budget Act of 2018 and planned for 2020 with the Affordable Care Act, and 5% in catastrophic phase, for each drug treatment across year). We observed that the use of coinsurance was high but consistent with the use of specialty / top tiering, similar to findings from a study using 2014 Part D formulary data for documenting coverage for other orally-administered anticancer medications.[40] Under the current Part D benefit, combined with the very-high per-fill prices for orally-administered anticancer drugs, expected out-of-pocket costs for advanced NSCLC patients with no low-income subsidy to initiate a single fill of a Part D treatment could be more than $3,300. As cancer regimens

increasingly consist of multiple drugs of different mechanisms (versus single-drug therapy) for potentially improved clinical benefits, our OOP estimates likely to understate the financial burden faced by patients.

On the other hand, we found that the prices of Part B drugs have been relatively stable over the same period. Part B drugs include traditional chemotherapies, the primary treatment strategy before targeted therapies increased options for advanced NSCLC. Among Part B drugs, older agents had consistently low prices (below $100/month) with the availability of generics while those older drugs in new formulations were priced substantially higher (to up to $8,000 for a month of treatment). Notably, immunotherapy, a new therapeutic class coming on market since 2015 for treating advanced NSCLC, is priced at more than ten thousand dollars per month, which is comparable to the price of orally administered targeted therapies under Part D. Since the average sales prices we used for Part B drugs already included rebates, we expect these drugs' prices could be even higher with a lower level of rebate.

Under the assumption of 20% coinsurance for part B (a typical amount on coinsurance asked for Part B services), the patient out-of-pocket cost for immunotherapies could also be several thousand a month. It is worth noting that more patients are eligible for immunotherapy than were ever for other targeted therapies covered under Part D (e.g., EGFR-targeted agents) and these immunotherapies are expensive, Part B drugs) could be the major cost driver in the near future. Importantly, when considering the financial impact and access for patients to Part B covered treatments, up to 85% of Part B enrollees have some form of supplemental insurance to cover their out-of-pocket spending.[26,27] This means that the vast majority of Medicare beneficiaries prescribed and initiating a Part B treatment will have good coverage that requires

little to no out-of-pocket spending. This is in contrast to Part D out-of-pocket protections which are available to only about 30% of all Part D enrollees.

Overall, our findings support our hypothesis on the drug-specific prices, formulary structure, and the use of utilization management tools for Part D medications approved for advanced NSCLC from 2009 to 2017. We found that over time prices of Part D advanced NSCLC drug have increased in excess of inflation; that over time these drugs are more likely to be placed on the highest drug tier or specialty drug tier within the formulary; that over time these drugs are more likely to require coinsurance (rather than copayments) for calculating patient cost-sharing; and that over time these are more likely to be subject to utilization management (e.g., step therapy, prior authorization, quantity limits).

5.2 AIM 2

In Aim 2, the goal was to examine the trends in the utilization of advanced NSCLC medications by coverage source (i.e., Medicare Part B or Part D). Particularly, we were interested in identifying clinical, sociodemographic, and health system factors associated with the use of Part D treatments among patients diagnosed with advanced NSCLC.

In this study, we found that the use of advanced NSCLC medications covered under Part D within the first year of diagnosis has been stable at around 10% and with slight decreases over the study period (2007-2014). This is true despite the approval of three new drugs (i.e., crizotinib, afatinib, ceritinib) during the study period evaluated. Although Part D treatments are usually indicated for cancer with specific genetic mutations, the use remains lower than expected based on the prevalence of gene mutations in the population (currently estimated to be around 15%)[208–213] in the advanced NSCLC population over time. Specifically, erlotinib accounted for

more than 90% of all use. This could be because erlotinib is the oldest drug with longest time of availability and more evidence on its clinical benefits. It might also reflect the broader indication for erlotinib; erlotinib was initially approved for unselected advanced NSCLC as second-line treatment (2004) or (maintenance treatment (2010) platinum-based chemotherapy (in 2016 the indication was restricted to EGFR mutant advanced NSCLC). In addition, a much higher prevalence of EGFR mutation, as compared to that of ALK mutation, may also contribute to the results. We have not observed the use of ceritinib possibly because it was approved in the last year of our study period (April, 2014) and was granted approval as a second-line therapy for metastatic ALK-positive NSCLC or due to the time lapse between approval and actual treatment adoption.

At the same time, the use of medications covered under Part B has slightly increased at around 45% of the advanced NSCLC population despite having only one new drug approved over the study period. The treatment rate has been improved since the 1990s when only 22 to 31% of patients with advanced NSCLC ever received chemotherapy.[145,146,214] Among Part B treatments, platinum-based regimens with traditional chemotherapies were the mainstream first-line treatments (almost 80% of the use). Particularly carboplatin-based regimens accounted for 65-70% of all use over time. Guidelines recommend platinum-based chemotherapy as the principle of systemic therapy for advanced and metastatic NSCLC.[51] In addition, most of the recommended systemic therapies consist of a platinum agent (i.e., carboplatin or cisplatin). This could be the reason why we observe this prevalent use of platinum-based regimens. Regimens with targeted therapy accounted for another 10-14% of all use. These findings are consistent with previous studies.[121,215]

Among the advanced NSCLC population, we observed more than 40% of the patients did not ever receive treatment, neither Part B nor Part D treatments, within the 12 months after diagnosis. These patients had lower social support (i.e., not marries) and poorer socioeconomic status (e.g., lower household income and education level at census tract level, more full LIS patients). In addition, these patients appeared to have poorer health status (e.g., higher comorbidity score or poorer disability score). We found that these patients had shorter survival time as compared to those who received treatments; the mean follow-up time since diagnosis were 7.5 and 15.3 months, respectively. It is possible that these patients did not have enough financial support to receive treatments. Patients might also decide not to take active treatments because of the poor prognosis of the cancer that curative treatments would not improve symptoms or extend survival much among these patients with advanced cancer. In the U.S., Medicare defines the need for hospice care at the end of life (with life expectancy of less than 6 months).[216] The focus of medical care for these patients with terminal lung cancer instead is to relieve symptom burden and enhance the quality of remaining life.[51,217]

In the examination of identifying key factors of Part D drug use, we found that many patient demographics, health status, tumor-related characteristics, and cost-sharing support are important in the use of Part D drug treatments following diagnosis of advanced NSCLC. We observed greater possibility of filling Part D drug prescription among adenocarcinoma histology, female sex, and "Other" race/ethnicity that includes Asians. These findings are consistent with previous research which suggested these are the most important factor associated with genetic mutation in NSCLC as well as the response to biological targeted therapies.[161,210,218] It is important to note that the choice between Part B and D treatments is likely to be driven by clinical details that are not available in the claims, such as EGFR.

Higher socioeconomic status was associated with higher possibility of Part D drug use; however, the effects were generally not significant after adjustment for other characteristics. Importantly, low-income subsidy, a federal cost-sharing assistance program that helps patients pay for Medicare Part D prescription drug costs, was associated with greater use of Part D drug treatments. This is especially true for those receiving full LIS. The association became even stronger when we restricted the examination to only treated patients (i.e., excluding patients who never received any Part B or Part D drugs within the year of diagnosis).

Overall, our findings do not affirm what we expect on the utilization of advanced NSCLC medications by coverage source (i.e., Medicare Part B or Part D). Instead of increases, we observed the use of advanced NSCLC medications covered under Part D has slightly decreased over the study period. On the other hand, we found a slight increase in the use of advanced NSCLC medications covered under Part B over the same period. Percentage of patients without any treatment remained stable over the study period.

5.3 AIM 3

In Aim 3, we examined the effect of low-income subsidies for Medicare Part D medications on treatment initiation among patients with advanced NSCLC. Through the propensity score adjustment and time-to-event analysis, we found that cost-sharing support for Part D treatment (e.g., novel targeted therapies) appears to be a key factor impacting the affordability and accessibility of advanced NSCLC care.

For Part D treatments, patients without full subsidy (i.e., non-LIS, partial LIS) were less likely to initiate Part D treatments as compared with those with full LIS. This is particularly true among the partial LIS group, who are not poor enough to receive the full subsidy and still

responsible for substantial amount of out-of-pocket cost for using Part D treatments despite their subsidy eligibility. The high upfront cost for initiating a Part D treatment may be limiting patient access to novel therapies. For a Part D drug priced at $14,000 per month, patients without cost-sharing support could be responsible for close to $3,000 for initiating the treatment (and approximately $700 out-of-pocket for the remaining monthly treatment even after they reach the catastrophic phase of coverage), whereas patients with full cost-sharing support pay less than $10 dollars for the same prescription. For those receiving the partial LIS, the cost of treatment could still reach almost $1000 for the first month for a single orally-administered anticancer presscription. Therefore, it is possible that patients without full cost-sharing support may delay their uptake of treatments while they seek funds to cover their drug cost. They may also settle for alternative treatments that have lower out-of-pocket costs.

Our findings are consistent with previous research showing delays in initiation of oral anticancer agents or treatments covered under Part D among individuals with high out-of-pocket cost and those without low-income subsidies.[114,170,219–221] Our results suggest that cost-sharing subsidies alleviate the financial barriers for Part D oral anticancer drug treatments and that the resulting difference in cost-sharing level appears to be associated with treatment uptake even after considering other important factors. Long-term health outcomes (e.g., survival), therefore, could be a concern without timely initiation of treatment in life-threatening conditions like advanced cancer. As the availability of oral anticancer treatment options continues to increase, access and affordability will be key determinants of the true benefit for patients.[221]

In our corresponding sensitivity analysis on Part B drug treatments (i.e., traditional chemotherapies), a negative control scenario where low out-of-pocket cost is expected for both LIS and non-LIS groups, we found that receiving LIS does not improve treatment uptake. For

Part B treatments, patients without any subsidy (i.e., non-LIS) instead were more likely to initiate Part B treatments compared to those with full subsidy or partial subsidy. This limited effect of subsidies could be due to the reasons that most patients have out-of-pocket coverage for Part B treatments so they face lower costs to start Part B treatments. Moreover, people who are non-LIS could even start the treatment earlier because they have more resources and thus are able to obtain supplemental health insurance to cover those cost-sharing requirements, which make them less disadvantaged than those who are Medicaid-eligible. Previous Patterns of Care (POC) analyses by the National Cancer Institute (NCI) indicated that cancer patients with Medicaid or Medicare-only were often under treated[222], which was confirm by several recent studies in the lung cancer population.[121,223,224] This disparity in NSCLC treatment particularly existed in patients with Medicaid or no insurance.[121,223,224] Our examination considered the low-income subsidy status, which separated out dual eligible and different levels of Medicaid, and extended the understanding to the realm of financial support in care.

In addition, the findings also provide robust support for our findings of financial barriers to timely initiation of therapy among cancer population; lack of appropriate cost-sharing support, either through subsidy programs or supplemental coverage, patient access to treatments was more restricted with the greater out-of-pocket cost burden, particularly for treatment initiation.

Overall, more attention should be paid towards affordable and equal access to high quality care for the advanced NSCLC population. Multiple factors contributing to high OOP costs for cancer patients, including high drug prices, benefit designs of health insurance (e.g., adoption specialty tier and coinsurance), and the increase in treatment complexity (e.g., combination therapy) could be avenues to reducing financial burden on patients. In the context of

current evolving health care reform, identifying fiscally sustainable strategies to improve patient affordability of and access to cancer medications is necessary.

Overall, our findings support our hypothesis on the effect of low-income subsidies for Medicare Part D medications on treatment initiation among patients with advanced NSCLC from 2007 to 2014. Specifically, we found that for Part D treatments, patients without full subsidy (i.e., non-LIS, partial LIS) were less likely to initiate Part D treatments as compared with those with full LIS. This is particularly true among the partial LIS group despite their subsidy eligibility. For Part B treatment, rather than no difference among groups, we found that patients without any subsidy (i.e., non-LIS) instead were more likely to initiate Part B treatments compared to those with full subsidy or partial subsidy. This finding provides robust support for our hypothesis that greater financial barriers are related to restricted access to treatment or reduced timely initiation of therapy among cancer population.

5.4 STRENGTHS AND LIMITATIONS

Our study has several limitations. First, genetic susceptibility could potentially influence the need for and response to treatment for NSCLC.[161,210,218] Unfortunately, information on genetic mutations and test results are not regularly collected in population-level registry-linked claim databases to date. However, the prevalence of gene mutations is not likely to vary by subsidy status, which minimizes the concern for Aim 3 of the study. It is critical that this information be incorporated in future studies as it becomes available to better understand who is eligible for therapy.

Secondly, given the nature of claims data, only filled prescriptions by patients could be observed. Therefore, we were not able to distinguish whether the difference in use was because

of physician prescribing behavior (the patient did not receive a prescription for a drug) or patient filling behavior (the patient received a prescription but did not fill the medication).

In addition, formulary information cannot be linked to current claims data available. Therefore, we were not able to determine the effects of Part D benefits designs on prescription drug uptake. Although some of the formulary features are provided in the SEER-Medicare prescription drug event (PDE) files (e.g., utilization management tools, benefit phase), we could only observe the information among patients who filled their prescriptions.

Lack of transparency in drug rebates is another limitation in our examination of Part D drug prices and patient out-of-pocket cost. In the current U.S. healthcare environment, the amount of rebate offered for Part D drugs is not required to be reported by plans, pharmacy benefit managers, or manufacturers and the amount could vary substantially. Greater transparency about the rebates could improve understanding of actual financial burden patients are facing from receiving essential treatments in the real world.

Lastly, due to the poor prognosis of lung cancer in general, some patients' health status might be too poor to use curative treatments or patients might die before any drug treatment is received during the observation period. In our examination, we also found that those without any treatments with infused chemotherapy (Part B) or oral targeted therapy (Part D) during the first year of diagnosis generally had shorter life or observation time; on average, about 7.5 months since diagnosis. For these patients, the focus of care might need to shift from an aggressive life-sustaining approach to an approach that prioritize symptom relief from the disease and achieves a better quality of life to the very end (e.g., palliative care).

There are, however, also several strengths of this study. This study used the most up-to-date data with detailed plan-level (or formulary-level) information, (e.g., plan benefit design,

cost share tier level, application of utilization management, and cost-sharing arrangement for drugs) to examine the difference in coverage offered and restrictions applied across all new and traditional advanced NSCLC treatments covered under Part D as of today. Notably, we provided expected out-of-pocket cost for initiating first month of anticancer treatment in NSCLC. This offers an overview of actual financial burden a patient could face for receiving care in current days.

In addition, to examine the real-world health outcomes among advanced NSCLC population, we used a large population-based data with a linkage between the SEER cancer registries and Medicare claims for the older population aged 65 or older. It provides detailed and nationally representative data on cancer and healthcare utilization data for Medicare patients with cancer. Since lung cancer is primarily a disease of older populations, this database affords a more detailed treatment analyses among this population.

Third, performance status is an important prognostic factor for survival and could affect potential treatment decisions. Given the limited availability of cancer performance status in the data, we applied a valid claim-based algorithm for older adults, predicted disability status as a proxy measure. This predicted disability status was considered as a key covariate in our two examinations (Aim 2 and 3) regarding the real-world treatment utilization among NSCLC population. The ability to assess disability status should improve covariate control and reduce indication bias. In addition, we further applied propensity scores to reduce the imbalance among groups, which helped alleviate potential bias in our results.

Notably, we used the examination of Part B drugs to complement the knowledge on currently available drug options in advanced NSCLC. We also used Part B drugs to serve as a

negative control for a robustness check in the investigation of the effect of high out-of-pocket spending on treatment uptake by subsidy status.

To our knowledge, this project is the first study to apply a disease-specific perspective for understanding the scope of care affordability and accessibility in NSCLC, a population with significant unmet needs. Beyond focusing on drug prices alone, we also consider diverse angles behind the growing patient financial burden in cancer care, including the benefit structure of plans as well as financial assistance in prescription drug expenses through the Medicare part D low income subsidy program. We are also the first study to consider and confirm the level of cost-sharing support (i.e., full subsidy, partial subsidy, and no subsidy) on possible gaps in treatment access – a crucial element to optimizing cancer care, particularly in advanced cancer settings.

5.5 CONCLUSION

Affordability of and accessibility to Part D treatments could continue to be a critical issue for advanced NSCLC patients with current plan benefits and ever-increasing drug prices. With more and more treatment breakthroughs for lung cancer emerging on the market combined with high launch drug prices and the aging of the U.S. population, out-of-pocket costs could present a considerable barrier to timely initiation of therapy among advanced NSCLC population. This is particularly true for those who are in need of treatments covered under Part D but do not have enough financial resources or support for receiving appropriate care. Restructure of Medicare's benefit design and enforcement mechanisms to control/monitor the drug pricing (e.g., value-based pricing) under Part D could be avenues to reducing financial burden on patients. In the context of current evolving health care reform, policy movement identifying

sustainable strategies to improve patient affordability of and equal access to high quality care are needed for the cancer population.

5.6 FUTURE RESEARCH

Due to the availability of data, the current study focused on the utilization of advanced NSCLC drugs between 2007 and 2014. Several years ago, the focus of drug development was oral drugs (covered under Part D). However, with the emerging role of immunotherapy for advanced NSCLC, infusion drugs (covered under Part B) are once again increasing in use. Immunotherapy differs from traditional chemotherapy (targets rapidly dividing cells, including healthy cells) and targeted therapies (interferes with key molecular in tumor cells to prevent tumor growth and invasion). It helps the immune system to recognize cancer, stimulates immune responsiveness, and relieves suppression of anti-tumor immunity. With an improved understanding of the immune system and advances in drug development, this newer immunotherapy appeared to be a promising treatment option in the management of advanced NSCLC. In addition, there are more patients eligible for immunotherapy than were ever for the targeted therapies. The first immunotherapy, Nivolumab (Opdivo®), was approved by the US FDA in 2015 for advanced NSCLC with progression on or after platinum-based chemotherapy in unselected populations. With the high prices of these drugs, Part B treatments may be a major cost burden to patients and society in the near future. Much work will be needed in this growing area – examining the affordability of and accessibility to novel high-priced drugs covered under Part B in addition to that in Part D. Further disentangling the factors behind the uptake of newer high-priced treatment by different coverage source (Part B or Part D) will potentially provide

more insights into the barriers to care and thus the approaches to improve appropriate care in the advanced NSCLC population.

In addition, genetic mutation is an important factor in the treatment decision and response to treatment in advanced NSCLC, such as EGFR or ALK-targeted agents. It is important for future research to incorporate the genetic information, if available, into the evaluation, as currently this information and related test results are not regularly collected in population-level registry-linked claim databases.

Among the three LIS groups, patients with partial LIS are still responsible for substantial amount of out-of-pocket cost for using Part D treatments (15% coinsurance) despite the subsidy eligibility. This group of patients tends to be those who have limited income and resources but are not poor enough to obtain full cost-sharing support for medical care. Our findings also suggest that the partial LIS group were particularly less likely to initiate Part D treatments despite their subsidy eligibility. Further investigation in the factors influencing the treatment uptake among these patients are needed, as most research to date has combined this subgroup into one subsidy group as a whole or excluded this subgroup from the examination.

In addition to assessing the treatment initiation, further research needs to be done to examine detailed treatment patterns among those who had initiated treatment. Particularly, analyses are needed on the role of low-income subsidy in the length of treatment (i.e., adherence or compliance). Whether the availability of more powerful but high-priced novel treatment options (e.g., oral targeted therapy, immunotherapy) would affect the continuance of current treatment regimen could be another area worth more research.

APPENDIX TABLES AND FIGURE

Appendix Table 3.1 Advanced Non-Small Cell Lung Cancer Drugs covered under Part D and approved by U.S. FDA by June 2017

Aim			Drug Name	Brand Name	Year of Approval		Therapeutic Class
					Cancer	NSCLC	
Aim 1	Aim 2	Aim 3	Gefitinib	Iressa	2003	2003[a] 2015	Targeted therapy – EGFR Tyrosine kinase inhibitor
			Erlotinib	Tarceva	2004	2004[b] 2010[b] 2013 2016[b]	Targeted therapy – EGFR Tyrosine kinase inhibitor[a]
			Crizotinib	Xalkori	2011	2011[c] 2016	Targeted therapy – ALK Tyrosine kinase inhibitor
			Afatinib	Gilotrif	2013	2013	Targeted therapy - EGFR Tyrosine kinase inhibitor
			Ceritinib	Zykadia	2014	2014	Targeted therapy – ALK Tyrosine kinase inhibitor
			Alectinib	Alecensa	2015	2015	Targeted therapy – ALK Tyrosine kinase inhibitor
			osimertinib	Tagrisso	2015	2015[d]	Targeted therapy – EGFR T790M Tyrosine kinase inhibitor

[a] On June 17, 2005, the U.S. Food and Drug Administration approved new labeling for gefitinib (Iressa®, a trademark of AstraZeneca) that limits the indication to cancer patients who, in the opinion of their treating physician, are currently benefiting, or have previously benefited, from gefitinib treatment. The decision is based on the data from two failed clinical studies of gefitinib that showed no survival benefit in the use of gefitinib among advanced NSCLC.

[b] As of October 2016, this indication is no longer FDA-approved. For NSCLC, the FDA-approval is limited to metastatic cancer that has certain epidermal growth factor receptor (EGFR) mutations.

[c] In 2011, accelerated approval for locally advanced or metastatic NSCLC that is anaplastic lymphoma kinase (ALK) -positive. In 2013, regular approval was granted for locally advanced or metastatic NSCLC that is ALK-positive.

[d] Accelerated approval in 2015 and full approval for NSCLC With a Specific EGFR Mutation in 2017.

[d] Specific NDC and HCPC codes are provided in **Appendix Table 3.3**.

[e] FDA gives thumbs up to Takeda's lung cancer drug. http://www.biopharmadive.com/news/fda-gives-thumbs-up-to-takedas-lung-cancer-drug/441653/

Abbreviation: ALK: Anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; mTOR: mammalian target of rapamycin; T790M: threonine at amino acid position 790

Appendix Table 3.2 Advanced Non-Small Cell Lung Cancer Drugs covered under Part B and approved by U.S. FDA by June 2017[a]

Aim			Drug Name	Brand Name	Year of Approval		Therapeutic Class
					Cancer	NSCLC	
Aim 1	Aim 2	Aim 3	Cistplatin	Platinol	1978	1994[b]	Traditional Chemo – Platinum-based agent
			Etoposide (VP-16)	Vepesid Etopophos	1983	N/A[c] N/A[d]	Traditional Chemo – DNA topoisomerase inhibitor
			Carboplatin	Paraplatin	1991	1999[c]	Traditional Chemo – Platinum-based agent
			Paclitaxel	Taxol Abraxane	1994	1998 2012	Traditional Chemo – Taxane
			Vinorelbine	Navelbine	1994	1994	Traditional Chemo – Vinca alkaloid and analog
			Docetaxel	Taxotere	1996	1999	Traditional Chemo – Taxane
			Gemcitabine	Gemzar	1996	1996	Traditional Chemo – Pyrimidine analog
			Pemetrexed	Alimta	2004	2008 2009	Traditional Chemo – Folate analog metabolic inhibitor (i.e., antifolate)
			Bevacizumab	Avastin	2004	2006	Targeted therapy – Monoclonal antibody on VEGF
			Ramucirumab	Cyramza	2014	2014	Targeted therapy – Monoclonal antibody on VEGF
			Nivolumab	Opdivo	2014	2015 2016	Targeted therapy/immunotherapy – PD-1 Inhibitor
			Pembrolizumab	Keytruda	2014	2015 2016	Targeted therapy/immunotherapy – PD-1 Inhibitor
			Necitumumab[b]	Portrazza	2015	2015	Targeted therapy/immunotherapy – monoclonal antibody on EGFR

[a] Specific NDC and HCPC codes are provided in **Appendix Table 3.4**.

[b] Indication for NSCLC is not specified in the cisplatin's labeling. However, within the approval of vinorelbine in 1994, cisplatin was used as combination treatment for advanced NSCLC.

[c] Indication for NSCLC is not specified in the etoposide's labeling. However, etoposide has long been recommended in combination use with platinum-based agent by the NCCN Guidelines.

[d] Indication for NSCLC is not specified in the carboplatin's labeling. However, within the approval of decetaxel in 1999, carboplatin was used as combination treatment for advanced NSCLC.

Abbreviation: EGFR: epidermal growth factor receptor; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; VEGF: Vascular endothelial growth factor.

Appendix Table 3.3 Oral Anticancer Drug for Advanced Non-Small Cell Lung Cancer by April 2017

Drug name	Brand Name	HCPCS[a]	NDC[a,b]	ATC[b]
Gefitinib	Iressa	J8565	00310048230	L01XE02
Erlotinib	Tarceva	N/A	50242006301, 54868547400, 50242006401, 54868544700, 50242006201, 54868529000	L01XE03
Crizotinib	Xalkori	N/A	00069814120, 00069814020	L01XE16
Afatinib	Gilotrif	N/A	00597014130, 00597013730, 00597013830	L01XE13
Ceritinib	Zykadia	N/A	00078064070	L01XE28
Alectinib	Alecensa	N/A	50242013001	L01XE36
Osimertinib	Tagrisso	N/A	00310134930, 00310135030	L01XE35

[a] HIPAA Space (https://www.hipaaspace.com/Medical_Billing/Coding/); HCPCS CODES (http://hcpcs.codes/)

[b] The Integrated Cancer Information and Surveillance System (ICISS, https://iciss.unc.edu); WHO Collaborating Centre for Drug Statistics Methodology, International language for drug utilization research – The Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) (https://www.whocc.no/atc_ddd_index/)

Abbreviation: HCPCS, Healthcare Common Procedure Coding System; NDC, National Drug Code; NSCLC: non-small cell lung cancer; ATC, the Anatomical Therapeutic Chemical Classification system by the World Health Organization Collaborating Centre (WHO).

Appendix Table 3.4 Infused Anticancer Drug for Advanced Non-Small Cell Lung Cancer by April 2017

Drug name	Brand Name	HCPCS[a]	NDC[a,b]	ATC [b]
Cisplatin	Platinol	J9060, J9062	00015322022, 00015322026, 00015322097, 00015322122, 00015322126, 00015322197, 00069008101, 00069008407, 00703574711, 00703574811, 10019091001, 10019091002, 16729028811, 16729028838, 44567050901, 44567051001, 44567051101, 55390009901, 55390011250, 55390011299, 55390018701, 55390041450, 55390041499, 63323010351, 63323010364, 63323010365, 63323010391, 63323010395, 67457042410, 67457042551, 68001028324, 68001028327, 68001028332, 68001028333, 62991284901, 62991284902	L01XA01
Etoposide (VP-16)	Vepesid	J8560, J9181, J9182	00015340420, 00013733691, 00013734694, 00013735688, 00703565301, 00703565601, 00703565691, 00703565701, 00703565791, 00015306120, 00015306124, 00015306220, 00015306224, 00015308420, 00015309520, 00015309530, 00015309595, 54569296300, 00015309145, 00074148501, 00074148502, 00074148503, 00074564301, 00074564601, 00074565301, 00074565601, 00074565701, 00074566701, 00186157131, 00209306022, 00209307020, 00209308020, 00209309020, 00364302853, 00703564301, 00703564601, 00703566701, 00703566801, 10019093001, 10019093002, 16729011408, 16729011411, 16729011431, 16729026231, 53905029101, 55390029101, 55390029201, 55390029301, 55390049101, 55390049201, 55390049301, 58406071112, 58406071418, 63323010405, 63323010425, 63323010450, 63323010465, 68001026522, 68001026523, 68001026524, 68001026525, 68001026526, 68001026527, 00378326694, 51079096501, 51079096505, 54569571800, 54868535500, 54868535502, 51927277200	L01CB01
Carboplatin	Paraplatin	J9045	00015321030, 00015321076, 00015321130, 00015321176, 00015321230, 00015321276, 00015321630, 00015321429, 00015321430, 00015321529, 00015321530, 00015321329, 00015321330, 00015323011, 00015323111, 00015323211, 00015323311, 00409112910, 00409112911, 00409112912, 00591333626, 00591333712, 00591333889, 00591345460, 00703324411, 00703324611, 00703324811, 00703324911, 00703423901, 00703423981, 00703424401, 00703424481, 00703424601, 00703424681, 00703424801, 00703424881, 00703424891, 10019091201, 10019091202, 10019091203, 10139006005, 10139006015, 10139006045, 15210006112, 15210006312, 15210006612, 15210006712, 25021020205, 25021020215, 25021020245, 25021020251, 47335015040, 47335015140, 47335028440, 47335030040, 55390015301, 55390015401, 55390015501, 55390015601, 55390022001, 55390022101, 55390022201, 61703033918, 61703033922, 61703033950, 61703033956, 61703033961, 61703033962, 61703033963, 61703036018, 61703036022, 61703036050, 63323016905, 63323016915, 63323016945, 63323017205, 63323017215, 63323017245, 63323017260, 66758004701, 66758004702 66758004703, 66758004704, 66860010001, 66860010101, 66860010201, 67457049154, 67457049215, 67457049346, 67457049461, 67457060820, 67817006112, 67817006312 67817006612, 67817006712, 00591222011, 00703326601, 00703327601, 10019091601, 10019091615, 50111096676, 55390015101, 63323016720, 63323016721, 00591368711 00703326801, 00703326871, 00703327801, 10019091701, 50111096776, 55390015201, 63323016800, 00591221911, 00703326401, 00703327401, 10019091501, 50111096576, 55390015001, 63323016610	L01XA02
Paclitaxel	Taxol	J9264, J9265	68817013450, 00172375377, 00172375396, 00172375473, 00172375494, 00172375531, 00172375576, 00172375675, 00172375695, 00015345620, 00015345699, 00015347520, 00015347527, 00015347530, 00015347620, 00015347627, 00015347630, 00015347911, 00069007601, 00069007801, 00069007901, 00074433501, 00074433502, 00074433504, 00555198414, 00555198514, 00703476401, 00703476481, 00703476601, 00703476681, 00703476701, 00703476801, 00703476881, 10518010207, 10518010208, 10518010209, 25021021305, 25021021317, 25021021350, 44567050501, 44567050601, 45963061353, 45963061356, 45963061359, 51079096101, 51079096201, 51079096301, 55390011405, 55390011420, 55390011450, 55390030405, 55390030420, 55390030450, 55390031405, 55390031420, 55390031450, 55390051405, 55390051420, 55390051450, 61703034209 61703034222, 61703034250, 63323076305, 63323076306, 63323076316, 63323076317, 63323076350, 63323076352, 66758004301, 66758004302, 66758004303, 67457043451, 67457044917, 67457047152	L01CD01

Vinorelbine	Navelbine	J9390	00081065601, 00081065644, 00173065601, 00173065644, 60831308601, 64370053201, 64370308601, 60831308602, 64370053202, 64370308602, 00069009901, 00069020510, 00703418201, 00703418281, 00703418291, 10019097001, 25021020401, 45963060755, 55390006901, 55390026701, 59911595801, 61703034106, 63323014801, 64370021001 66758004501, 67457043111, 67457048101, 00069010303, 00069020550, 00703418301, 00703418381, 00703418391, 10019097002, 25021020405, 45963060756, 55390007001, 55390026801, 59911595901, 61703034109, 63323014805, 64370025001, 66758004502, 67457047953	L01CA04
Docetaxel	Taxotere	J9170, J9171	47335028541, 47335028641, 00075800301, 00075800404, 00075800120, 00075800180, 00069914411, 00409020120, 00409020127, 66758005003, 66758095004, 00955102208 16729023165, 16729026765, 42367012129 45963079056, 00409036601, 00703572001, 00955102001, 16714046501, 16729023163, 16729026763, 25021022201, 42367012121, 43598025811, 45963073454, 63739093211, 00069914111, 00069914122, 00409020102, 00409020125, 66758005001, 66758095002, 00409036701, 00703573001, 00955102104, 16714050001, 16729023164, 16729026764, 25021022204, 42367012125, 43598025940, 45963073452, 45963076552, 63739097117, 00069914211, 00069914222, 00409020110, 00409020126, 66758005002, 66758095003, 25021022207, 45963073474, 16729012049, 60505603500, 60505603506, 16729022850, 60505603700, 60505603706	L01CD02
Gemcitabine	Gemzar	J9201	00002750201, 00002750101, 00069385810, 00409018601, 00591356355, 00703577801, 00781328379, 16729011711, 23155021431, 23155048431, 23155052931, 25021020950, 25021023550, 45963061959, 47335015440, 55111068725, 55390039150, 63323012550 63323012553, 63323012594, 67457046201, 68001028223, 68001028226, 00409018101, 00409018125, 45963062458, 00069385910, 00409018701, 16729011838, 45963062060, 63323012600, 67457046302, 68001028224, 68001028227, 00409018201, 00409018225, 45963063660, 00069385710, 00409018501, 00591356279, 00703577501, 00781328275, 16729009203, 23155021331, 23155048331, 23155052831, 25021020810, 25021023410, 45963061257, 47335015340, 55111068607, 55390039110, 63323010210, 63323010213, 63323010294, 67457046420, 68001028222, 68001028225, 00409018301, 00409018325, 45963062357	L01BC05
Pemetrexed	Alimta	J9305	00002764001 00002762301	L01BA04
Bevacizumab	Avastin	J9035, C9257, Q2024	50242006001 50242006002 50242006101 70360000102	L01XC07
Ramucirumab	Cyramza	J9308, C9025[c] J9999, J3490, J3590	00002766901 00002767801	L01XC21
Nivolumab	Opdivo	J9299, C9453[d] J9999, J3490, J3590	00003377211 00003377412	L01XC17
Pembrolizumab	Keytruda	J9271, C9027[e]	00006302601 00006302602 00006302901 00006302902	L01XC18

		J9999, J3490, J3590		
Necitumumab[f]	Portrazza	J9295, C9475[f] J9999, J3490, J3590	00002771601	L01XC22

Abbreviation: HCPCS, Healthcare Common Procedure Coding System; NDC, National Drug Code; NSCLC: non-small cell lung cancer; ATC, the Anatomical Therapeutic Chemical Classification system by the World Health Organization Collaborating Centre (WHO).

Note: J9999, J3490,and J3590 are unspecified codes used before specific codes available for the approved drugs.

[a] HIPAASpace (https://www.hipaaspace.com/Medical_Billing/Coding/); HCPCS CODES (http://hcpcs.codes/)

[b] The Integrated Cancer Information and Surveillance System (ICISS, https://iciss.unc.edu); WHO Collaborating Centre for Drug Statistics Methodology, International language for drug utilization research – The Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) (https://www.whocc.no/atc_ddd_index/)

[c] Coding information: https://www.accc-cancer.org/ossn_network/pdf/cyramza-announcement.pdf

[d] Coding information: http://www.bmsaccesssupport.bmscustomerconnect.com/servlet/servlet.FileDownload?file=00Pi000000FtTI9EAN;

[e] Coding information: https://www.merckaccessprogram-keytruda.com/static/pdf/keytruda-billing-ndc-codes.pdf; https://www2.ncdhhs.gov/DMA/bulletin/0115bulletin.htm#keytruda

[f] Code information: http://www.lillypatientone.com/portrazza.html; http://www.portrazza.com/assets/img/_pdfs/Portrazza-Billing-and-Coding-Guide.pdf

Appendix Table 3.5 Summary of Surgery for Non-Small Cell Lung Cancer

	Healthcare Common Procedure Coding System (HCPCS)	International Classification of Diseases, 9th revision – Procedure (ICD-9-Procedure)
Surgery		
Biopsy	31625, 31628, 31629, 31632, 31633, 32095, 32400, 32402, 32405, 32602, 32604, 32606, 32607, 32608, 32609, 30900, 30910, 30920, 39400, 76360, 31641,	33.24-33.28, 34.02-34.27, 40.11
Local excision	32442, 32480, 32482, 32484, 32486,	32.2, 32.2x
Resection	32488, 32500, 32503, 32520, 32522, 32525, 32657, 32663, 32440, 32445, 32450, 32485, 32490, 32491, 32501, 32504-32507	32.3, 32.3x, 32.4, 32.4x, 32.5, 32.5x, 32.6, 32.9

Appendix Table 3.6 Summary of Radiation Therapy for Non-Small Cell Lung Cancer

	HCPCS)	ICD-9-Procedure	ICD-9-CM	Additional codes
Any Radiation Therapy	77520, 77523, 774xx, 7775x, 7776x, 7777x, 7778x, 7779x	92.2x	V58.0, V66.1 V67.1	Revenue Center: 0330, 0333

Abbreviation: HCPCS, Healthcare Common Procedure Coding System; ICD-9-Procedure, International Classification of Diseases, 9th revision – Procedure; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification.

Appendix Table 4.1 Median Prices of Advanced Non-Small Cell Lung Cancer Drugs Covered under Part D, 2010Q1-2017Q1 (2017 USD)

	2010Q1	*2011Q1*	*2012Q1*	*2013Q1*	*2014Q1*	*2015Q1*	*2016Q1*	*2017Q1*
	median (min, max)	median (min, max)	median (min, max)	median (min, max)	median (min, max)	median (min, max)	median (min, max)	median (min, max)
ERLOTINIB								
25 MG	$3,479.6 ($2,766.1, $4,053.3)	$3,533.9 ($1.3, $4,376.2)	$3,955.8 ($1.4, $4,413.6)	$4,497.9 ($3,209.5, $4,960.7)	$4,747.0 ($3,182.4, $5,126.8)	$4,828.1 ($4,613.9, $5,314.7)	$5,030.4 ($4,657.9, $5,952.6)	$5,109.5 ($4,546.8, $6,245.9)
100 MG	$4,776.8 ($4,032.0, $5,738.1)	$4,858.7 ($1.3, $5,788.2)	$5,432.5 ($1.4, $6,616.5)	$6,148.8 ($5,238.0, $6,808.4)	$6,505.9 ($5,782.7, $7,262.7)	$6,619.6 ($6,111.7, $7,434.5)	$6,890.2 ($6,295.3, $7,483.8)	$6,999.9 ($6,389.2, $7,626.3)
150 MG	**$5,405.0 ($3,596.4, $6,231.1)**	**$5,506.7 ($1.3, $6,546.5)**	**$6,147.1 ($1.4, $6,945.2)**	**$6,955.0 ($5,791.7, $7,835.9)**	**$7,357.7 ($6,318.3, $8,207.1)**	**$7,483.1 ($6,123.2, $8,401.4)**	**$7,789.8 ($6,474.1, $8,970.5)**	**$7,913.7 ($5,381.0, $9,267.1**
GEFITINIB								
250 MG	**$2,295.9 ($1,820.2, $3,408.7)**	**$2,210.5 ($1,864.0, $2,481.6)**	**$2,123.1 ($1,596.6, $2,320.8)**				**$7,991.2 ($7,479.8, $8,507.7)**	**$7,898.2 ($7,347.4 $8,369.1)**
CRIZOTINIB								
250 MG			**$ 11,842.7 ($1.4, $12,478.2)**	**$12,691.4 ($8,344.4, $14,412.0)**	**$13,678.6 ($12,127.6, $14,630.9)**	**$14,560.2 ($12,914.7, $16,878.5)**	**$15,348.8 ($13,755.6, $18,041.5)**	**$15,123.6 ($13,362.3, $16,364.1)**
200 MG			$ 11,842.7 ($1.4, $12,478.2)	$12,694.0 ($ 11,635.2, 14,563.4)	$13,821.1 ($12,402.5, $14,520.2)	$14,566.9 ($13,207.1, $16,878.5)	$15,455.3 ($12,532.6, $16,622.7)	$15,210.5 ($13,362.3, $16,353.5)
AFATINIB								
30 MG						$7,373.7 ($7,081.5, $7,880.4)	$7,699.7 ($5,112.0, $8,220.1)	$7,702.7 ($6,796.6, $8,322.2)
40 MG						**$7,373.7 ($7,081.5, $7,880.4)**	**$7,634.6 ($6,955.9, $8,178.9)**	**$7,684.0 ($6,796.6, $8,322.2)**
20 MG						$7,373.7 ($7,081.5, $7,880.4)	$7,686.1 ($6,955.9, $8,178.9)	$7,699.1 ($6,796.6, $8,322.2)
CERITINIB								
150 MG						**$15,373.4 ($14,764.0, $16,430.1)**	**$14,905.3 ($13,425.3, $15,869.1)**	**$15,384.0 ($14,160.2, $16,610.8)**
ALECTINIB								
150 MG							**$13,605.2 ($12,261.5, $14,493.1)**	**$13,798.0 ($12,581.9, $14,664.4)**
OSIMERTINIB								
40 MG							$14,079.6 ($12,681.7, $14,989.9)	$14,707.0 ($13,410.5, $15,630.5)
80 MG							**$14,079.6 ($12,681.7, $14,989.9)**	**$14,707.0 ($13,410.5, $15,630.5)**

Appendix Table 4.2 Average Sales Prices for Advanced NSCLC Drugs Covered under Part B (2017 USD)

GENERIC NAME	STRENGTH & FORMULATION	2010Q1	2011Q1	2012Q1	2013Q1	2014Q1	2015Q1	2016Q1	2017Q1	NOTES
CISPLATIN	10 MG IV	$52.46	$53.1	$41.4	$48.4	$46.9	$46.7	$32.21	$40.5	
CISPLATIN	50 MG IV	$52.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	J code not available since 2011
ETOPOSIDE (VP-16)	50 MG PO	$2,512.8	$2,403.0	$3,117.2	$3,945.3	$4,373.0	$4,010.4	$4,690.8	$4,728.4	
ETOPOSIDE (VP-16)	10 MG IV	$44.9	$70.5	$71.0	$72.2	$65.9	$56.9	$52.4	$48.4	
CARBOPLATIN	50 MG IV	$79.2	$60.4	$63.7	$48.9	$46.3	$49.3	$49.0	$46.0	
PACLITAXEL	1 MG albumin-bound	$9,453.0	$9,090.7	$8,955.5	$8,708.6	$8,598.6	$8,293.2	$8,328.1	$8,081.3	
PACLITAXEL	30 MG IV	$142.7	$102.0	$105.3	$78.6	$59.3				J code not valid since 2015
PACLITAXEL	1 MG IV						$62.0	$57.2	$63.9	J code valid since January 2015
VINORELBINE	10 MG IV	$194.7	$212.1	$179.7	$168.7	$143.5	$148.4	$152.2	$113.6	
DOCETAXEL	1 MG IV	$4,441.5	$4,469.7	$3,244.9	$1,457.8	$1,045.5	$852.5	$538.5	$499.0	
GEMCITABINE	200 MG IV	$4,870.5	$4,906.9	$1,586.7	$331.1	$222.9	$203.2	$241.2	$144.5	
PEMETREXED	10 MG IV	$8,499.7	$8,460.7	$8,533.2	$8,853.2	$9,043.0	$8,660.5	$8,544.2	$8,035.5	
BEVACIZUMAB	10 MG IV	$11,925.7	$11,915.5	$11,695.7	$11,951.4	$12,210.6	$11,967.6	$12,106.6	$11,849.4	
RAMUCIRUMAB	5 MG IV							$12,307.9	$12,083.1	J code valid since January 2016
NIVOLUMAB	1 MG IV							$14,865.0	$14,353.1	J code valid since January 2016
PEMBROLIZUMAB	1 MG IV							$10,412.1	$9,973.6	J code valid since January 2016
NECITUMUMAB	1 MG IV								$12,870.0	J code valid since January 2017

Abbreviation: IV, injection; PO: oral administration.

Appendix Table 4.3 Coverage of Advanced Non-Small Cell Lung Cancer Drugs among Part D Plans, 2010Q1-2017Q1.

	2010Q1				*2011Q1*				*2012Q1*				*2013Q1*				*2014Q1*				*2015Q1*				*2016Q1*				*2017Q1*			
	MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs	
# of plans on the market	N=1908		N=1594		N=1642		N=1136		N=1699		N=1063		N=1768		N=1051		N=1787		N=1186		N=1867		N=1013		N=1950		N=897		N=2031		N=757	
Plans covering all therapeutic classes covered	1778	93.2%	1533	96.2%	1252	76.2%	885	77.9%	1646	96.9%	1061	99.8%	1765	99.8%	951	90.5%	1766	98.8%	1111	93.7%	1857	99.5%	1013	100.0%	1942	99.6%	897	100.0%	1984	97.7%	689	91.0%
Plans covering ll drugs covered	1401	73.4%	1035	64.9%	1074	65.4%	665	58.5%	1370	80.6%	784	73.8%	1765	99.8%	951	90.5%	1766	98.8%	1111	93.7%	1857	99.5%	1013	100.0%	1824	93.5%	897	100.0%	1984	97.7%	689	91.0%
Plans covering erlotinib	1778	93.2%	1533	96.2%	1252	76.2%	885	77.9%	1646	96.9%	1061	99.8%	1765	99.8%	951	90.5%	1766	98.8%	1111	93.7%	1857	99.5%	1013	100.0%	1942	99.6%	897	100.0%	1984	97.7%	689	91.0%
Plans covering gefitinib	1401	73%	1035	65%	1074	65%	665	59%	1370	81%	784	74%													1942	100%	897	100%	1984	98%	689	91%
Plans covering crizotinib									1646	96.9%	1061	99.8%	1765	99.8%	951	90.5%	1766	98.8%	1111	93.7%	1857	99.5%	1013	100.0%	1942	99.6%	897	100.0%	1984	97.7%	689	91.0%
Plans covering afatinib																					1857	99.5%	1013	100.0%	1942	99.6%	897	100.0%	1984	97.7%	689	91.0%
Plans covering certinib																					1857	99.5%	1013	100.0%	1942	99.6%	897	100.0%	1984	97.7%	689	91.0%
Plans covering alectinib																									1824	93.5%	897	100.0%	1984	97.7%	689	91.0%
Plans covering osimertinib																									1885	96.7%	897	100.0%	1984	97.7%	689	91.0%

Appendix Table 4.4 Application of Utilization Management Tools and Drug Tiering in Part D Plans, by Drug, 2010Q1-2017Q1

	2010Q1				2011Q1				2012Q1				2013Q1				2014Q1				2015Q1				2016Q1				2017Q1			
PLANS COVERING ERLOTINIB																																
	MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs	
	N=1778		**N=1533**		**N=1252**		**N=885**		**N=1646**		**N=1061**		**N=1765**		**N=951**		**N=1766**		**N=1111**		**N=1857**		**N=1013**		**N=1942**		**N=897**		**N=1984**		**N=689**	
PA	1325	75%	1268	83%	998	80%	772	87%	1210	74%	843	79%	1393	79%	803	84%	1505	85%	972	87%	1594	86%	1012	100%	1701	88%	897	100%	1736	88%	689	100%
ST	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
QL	658	37%	663	43%	589	47%	384	43%	749	46%	488	46%	907	51%	609	64%	859	49%	675	61%	999	54%	627	62%	1092	56%	503	56%	1434	72%	541	79%
Top Tier	1690	95%	1455	95%	1220	97%	883	100%	1543	94%	1032	97%	1623	92%	947	100%	1515	86%	1011	91%	1607	87%	975	96%	1647	85%	860	96%	1659	84%	652	95%
Specialty Tier	1663	94%	1204	79%	1189	95%	741	84%	1562	95%	926	87%	1677	95%	843	89%	1661	94%	1036	93%	1697	91%	977	96%	1816	94%	897	100%	1880	95%	689	100%
PLANS COVERING GEFITINIB																																
	MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs	
	N=1401		**N=1035**		**N=1074**		**N=665**		**N=1370**		**N=784**														**N=1942**		**N=897**		**N=1984**		**N=689**	
PA	352	25%	259	25%	197	18%	147	22%	280	20%	142	18%													1613	83%	858	96%	1673	84%	654	95%
ST	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%													0	0%	0	0%	0	0%	0	0%
QL	529	38%	285	28%	563	52%	273	41%	651	48%	270	34%													1216	63%	567	63%	1245	63%	448	65%
Top Tier	1286	92%	911	88%	1030	96%	625	94%	1252	91%	718	92%													1639	84%	786	88%	1660	84%	582	84%
Specialty Tier	1262	90%	839	81%	989	92%	555	83%	1284	94%	647	83%													1813	93%	823	92%	1832	92%	619	90%
PLANS COVERING CRIZOTINIB																																
									MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs		MAs		PDPs	
									N=1646		**N=1061**		**N=1765**		**N=951**		**N=1766**		**N=1111**		**N=1857**		**N=1013**		**N=1942**		**N=897**		**N=1984**		**N=689**	

	PA	1468	89%	933	88%	1561	88%	891	94%	1575	89%	1005	90%	1672	90%	1013	100%	1784	92%	897	100%	1840	93%	689	100%
	ST	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
	QL	861	52%	617	58%	986	56%	630	66%	1005	57%	682	61%	1079	58%	671	66%	1148	59%	489	55%	1176	59%	382	55%
	Top Tier	1540	94%	1030	97%	1645	93%	947	100%	1531	87%	1011	91%	1612	87%	975	96%	1647	85%	860	96%	1664	84%	652	95%
	Specialty Tier	1553	94%	924	87%	1682	95%	843	89%	1670	95%	1036	93%	1705	92%	977	96%	1821	94%	897	100%	1886	95%	689	100%
PLANS COVERING AFATINIB																									
														MAs		PDPs		MAs		PDPs		MAs		PDPs	
														N=1857		**N=1013**		**N=1942**		**N=897**		**N=1984**		**N=689**	
	PA													1682	91%	1013	100%	1795	92%	897	100%	1843	93%	689	100%
	ST													0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
	QL													1050	57%	689	68%	1136	58%	573	64%	1180	59%	402	58%
	Top Tier													1612	87%	969	96%	1647	85%	860	96%	1664	84%	652	95%
	Specialty Tier													1705	92%	971	96%	1821	94%	897	100%	1886	95%	689	100%
PLANS COVERING CERITINIB																									
														MAs		PDPs		MAs		PDPs		MAs		PDPs	
														N=1857		**N=1013**		**N=1942**		**N=897**		**N=1984**		**N=689**	
	PA													1685	91%	967	95%	1789	92%	840	94%	1881	95%	678	98%
	ST													0	0%	0	0%	3	0%	0	0%	0	0%	0	0%
	QL													1120	60%	657	65%	1234	64%	576	64%	1323	67%	517	75%

Top Tier	1594	86%	1007	99%	1645	85%	856	95%	1656	83%	652	95%
Specialty Tier	1702	92%	1009	100%	1819	94%	893	100%	1878	95%	689	100%

PLANS COVERING ALECTINIB

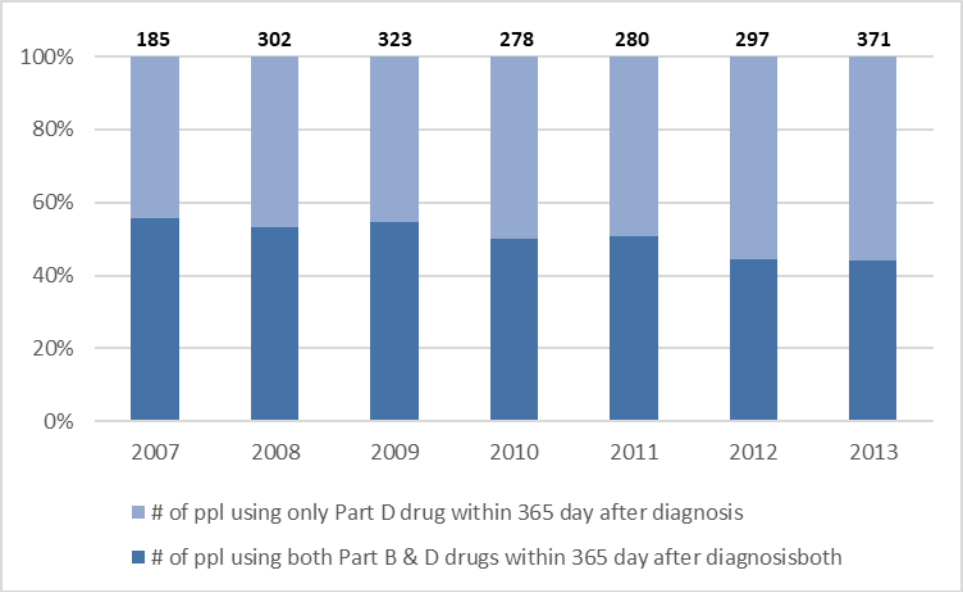
	MAs		PDPs		MAs		PDPs	
	N=1824		**N=897**		**N=1984**		**N=689**	
PA	1567	86%	860	96%	1747	88%	631	92%
ST	3	0%	0	0%	0	0%	0	0%
QL	1192	65%	571	64%	1269	64%	472	69%
Top Tier	1599	88%	786	88%	1662	84%	546	79%
Specialty Tier	1707	94%	823	92%	1884	95%	583	85%

PLANS COVERING OSIMERTINIB

	MAs		PDPs		MAs		PDPs	
	N=1885		**N=897**		**N=1984**		**N=689**	
PA	1736	92%	893	100%	1826	92%	689	100%
ST	0	0%	0	0%	0	0%	0	0%
QL	1382	73%	604	67%	1422	72%	505	73%
Top Tier	1617	86%	856	95%	1664	84%	652	95%
Specialty Tier	1756	93%	893	100%	1885	95%	689	100%

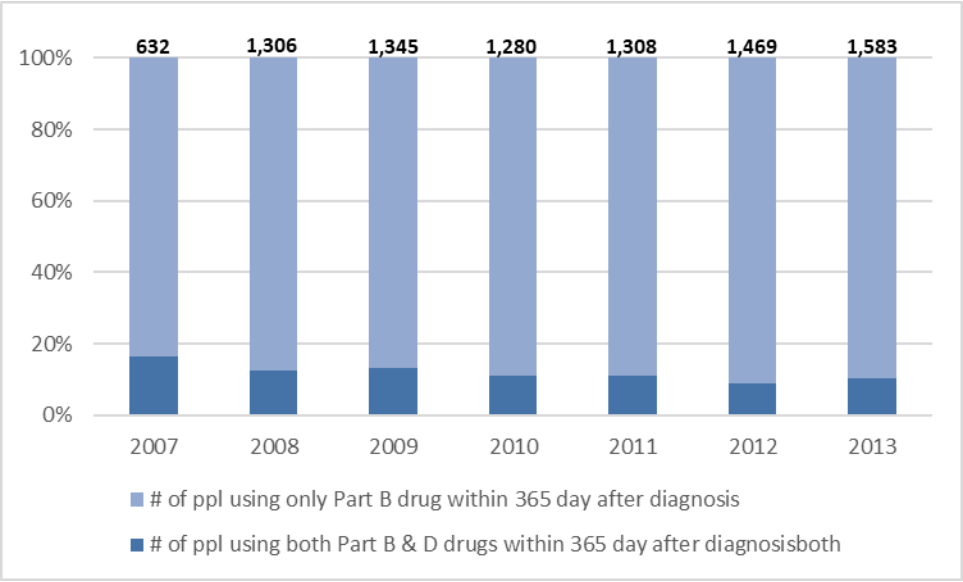
Abbreviation: PA: prior authorization; QL: quantity limit; ST: step therapy.

Appendix Figure 4.1A Composition of NSCLC Drugs Utilization on Medicare Part D within 12-month after Diagnosis of Advanced NSCLC, 2007-2014[a]



[a] The numbers above the bars indicates the total number of people ever using a Part D drug during the 12-month period after Diagnosis of Advanced NSCLC

Appendix Figure 4.1B. Composition of NSCLC Drugs Utilization on Medicare Part B within 12-month after Diagnosis of Advanced NSCLC, 2007-2014[a]



[a] The numbers above the bars indicates the total number of people ever using a Part B drug during the 12-month period after Diagnosis of Advanced NSCLC

Appendix Table 4.5 Standard Differences Before and After Inverse Probability of Treatment Weighting (IPTW)

		Standardized difference[a]			
		Before IPTW		After IPTW	
		Partial vs Full	Non vs Full	Partial vs Full	Non vs Full
Age		0.0776	0.1483	0.0349	0.0708
Sex		0.0190	0.0401	-0.0047	0.0085
Race/Ethnicity		0.5137	0.8849	0.0645	0.0488
Marital Status		0.0836	0.5108	0.0124	0.0598
Region		0.6018	0.4135	0.0599	0.1085
Urban/Rural Residence		0.1889	0.0910	0.0252	0.0402
Census Tract % of Non-High School Degree		0.2305	0.8145	0.0207	0.0633
Census Tract % below poverty		0.2449	0.7370	0.0240	0.0754
Census Tract Household Median Income		0.1374	0.6526	0.0197	0.0942
Comorbidity Index		0.1229	0.2507	0.0027	0.0621
Predicted DS		-0.3652	-0.4119	0.0050	-0.0282
Year of Diagnosis		0.1595	0.1067	0.0213	0.0543
Quarter of Year of Diagnosis		0.0490	0.0171	0.0102	0.0478
Cancer Stage		0.1125	0.2003	-0.0009	0.0248
Cancer Histology					
	Adenocarcinoma	-0.0411	0.1222	0.0079	0.0119
	Squamous	0.0075	-0.1348	-0.0011	0.0096
	Large cell	0.0059	0.0093	-0.0031	-0.0015
	Others	0.0403	-0.0067	-0.0075	-0.0251
Radiation as First Course of Therapy		0.1156	0.1563	0.0229	0.0528
Surgery as First Course of Therapy		0.0356	0.1070	0.0201	0.0416
Receipt of Care from Hospital Affiliation with					
	NCI Designation	-0.0524	0.1490	-0.0145	-0.0358
	ECOG	0.1970	0.2684	-0.0085	-0.0844
	Teaching Hospital	0.0246	0.1000	0.0049	-0.0392
	Major Affiliation with Medical School	0.1441	0.1684	-0.0037	-0.0386

[a] Standardized difference[197] represents the difference in the means of two groups in units of standard deviation of the variable. The values allow for an assessment of differences between two groups. As a rule of thumb, standardized differences greater than 0.10. indicate a meaningful imbalance in the baseline covariate. For this study, the standardized mean differences post IPTW were all below 0.10 between groups (Non-LIS vs Full LIS; Partial LIS vs LIS), suggesting negligible imbalance in patient baseline characteristics between groups for the analysis.
Abbreviation: 95% CI, 95% Confidence Interval; DS, Disability Status; ECOG: the Eastern Cooperative Oncology Group; LIS: Low Income Subsidy; NSCLC: Non-Small Cell Lung Cancer.

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