THE USE, EFFECTIVENESS, AND SAFETY OF BEVACIZUMAB IN OLDER ADULTS WITH ADVANCED STAGE NON-SMALL CELL LUNG CANCER

Aaron Jacob Katz

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Division of Pharmaceutical Outcomes and Policy, UNC Eshelman School of Pharmacy

Chapel Hill
2012

Approved by:

Joel F. Farley, PhD

William R. Carpenter, PhD

Lynn G. Dressler, DrPH

Betsy L. Sleath, PhD

Thomas E. Stinchcombe, MD

ABSTRACT

AARON JACOB KATZ: The Use, Effectiveness, and Safety of Bevacizumab In Older Adults With Advanced Stage Non-Small Cell Lung Cancer
(Under the direction of Joel F. Farley, PhD)

Background: In clinical trials, the addition of bevacizumab to standard platinum-based doublet chemotherapy significantly improved overall survival in patients with advanced non-small cell lung cancer (NSCLC). However, a significant survival advantage with bevacizumab was not detected in subsequent analyses of patients aged 65 years and older.

Objectives: To identify patient and health system characteristics associated with the use of bevacizumab and evaluate its effectiveness and safety in older patients with advanced NSCLC.

Methods: Retrospective cohort study of adults 66 years or older identified within the Surveillance, Epidemiology, and End Results (SEER)-Medicare database with a diagnosis of stage IIIB or stage IV non-squamous NSCLC between 2004 and 2007. Descriptive statistics were used to characterize the utilization of bevacizumab. Multivariable logistic regression models were run to estimate the odds of bevacizumab use based on patient demographic, clinical, and health system characteristics. Logistic regression and Cox proportional hazards models were used to evaluate the effect of adding bevacizumab to platinum-based doublet chemotherapy on overall survival and hospitalization for severe treatment-related adverse events.

Results: Clinical characteristics including stage of disease and comorbidity burden as well as receipt of chemotherapy from a provider affiliated with the National Cancer Institute's (NCI) Community Clinical Oncology Program (CCOP) were independent predictors of the use of bevacizumab. Median

survival was 9.8 months among patients receiving bevacizumab plus platinum-based doublet chemotherapy and 8.9 months among patients receiving chemotherapy alone (hazard ratio [HR], 1.02; 95% CI, 0.91 to 1.13; P = 0.76). Neither multivariable nor propensity score-adjusted Cox models demonstrated a survival advantage with the addition of bevacizumab to platinum-based chemotherapy. Compared to platinum-based doublet chemotherapy alone, the addition of bevacizumab was associated with a higher incidence of hospitalization for any severe treatment-related adverse event (10% vs. 14%, respectively; P = 0.003); however, this association was not statistically significant after adjusting for confounders in a multivariable-adjusted Cox proportional hazards model (HR, 1.31; 95% CI, 0.94 to 1.79).

Conclusions: Patient clinical characteristics and provider affiliation with the CCOP were important predictors of bevacizumab use. However, adding bevacizumab to platinum-based doublet chemotherapy was not associated with better survival among Medicare patients with advanced NSCLC.

ACKNOWLEDGEMENTS

First and foremost I would like to thank my wife Kerry for her constant support during my educational journey. Your sacrifices allowed me to pursue a graduate education while your encouragement provided the motivation I needed to be successful; I could not have come this far without you by my side. I would also like to thank my parents for their unremitting confidence in my abilities and their tireless support of my educational endeavors as well as teaching me early on in life about the importance of knowledge and learning. Thank you as well to all of my family and friends for their endless support and praise. In particular, thank you Justin for opening my eyes to the possibility of graduate school and inspiring me down a path I might not otherwise have traveled. Thank you Stacie and Patrick for your constant guidance, mentoring, and friendship; you both made graduate school a fun and rewarding experience.

I would like to acknowledge my adviser Dr. Joel Farley for his continuous guidance and support throughout my graduate studies. Your mentorship inspired me to challenge myself and has made me a better researcher. Thank you for tolerating my quirkiness and for pushing me when I needed to be shoved. I would also like to acknowledge Drs. Bill Carpenter, Lynn Dressler, Betsy Sleath, and Tom Stinchcombe for their contributions to my education and their willingness to support and guide me in the development of my dissertation. Thank you to my previous advisers Drs. Mick Murray and Rick Hansen for their support and guidance during my initial time in the graduate program. I would also like to acknowledge Dr. Peggye Dilworth-Anderson for her valuable mentorship during my time as a pre-doctoral fellow at the UNC Institute on Aging.

TABLE OF CONTENTS

LIST OF TABLES

Table

LIST OF FIGURES

Figure

LIST OF ABBREVIATIONS

AJCC	American Joint Committee on Cancer
ATE	Arterial thromboembolic events
CCOP	Clinical Community Oncology Program of the National Cancer Institute
CHF	Congestive heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disorder
CVD	Cerebrovascular disease
DM	Diabetes mellitus
ECOG	Eastern Cooperative Oncology Group
GI	Gastrointestinal
HR	Hazard ratio
MI	Myocardial infarction
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OR	Odds ratio
PVD	Peripheral vascular disease
SEER	Surveillance, Epidemiology, and End Results

CHAPTER ONE

INTRODUCTION

1.1 Overview

Lung cancer is the second most common form of cancer among men and women and is the leading cause of cancer-related deaths in the United States.[1] With a median age of 71 years at diagnosis and over 70% of newly diagnosed patients at least 65 years of age, lung cancer is a disease that occurs primarily in older adults.[2] Approximately 85% of lung cancer diagnoses are of the non-small cell lung cancer type (NSCLC) and the majority of patients present with locally advanced or metastatic disease at the time of diagnosis, contributing to a poor survival rate.[2] Platinum-based doublet chemotherapy is the standard treatment for patients with advanced stage disease and has been shown to lessen cancer-related symptoms, lengthen survival, and improve quality of life. However, the overall survival benefit from chemotherapy for most patients with advanced NSCLC remains poor with a median progression-free survival of approximately 4-5 months and median overall survival around 8-11 months.[3,4] In addition, chemotherapy is associated with toxic adverse effects that may be especially problematic for older adults and patients with poor overall health. As a result, efforts have been dedicated toward developing targeted treatments that direct their effect toward tumor-specific characteristics, have greater activity at the cancer site, and result in lower systemic toxicity compared to standard chemotherapy.

Bevacizumab is the only monoclonal antibody currently approved in addition to chemotherapy for the first-line treatment of advanced NSCLC in the United States. Knowledge about the efficacy and safety of bevacizumab generally stems from the results of several clinical trials that

show bevacizumab improves response rate, progression-free survival, and overall survival beyond that of standard platinum-based chemotherapy alone; however, bevacizumab is also associated with a prohibitive rate of life-threatening or fatal pulmonary hemorrhage in patients with squamous histology, thus its use is limited to patients with non-squamous histology tumors. Still, although most lung cancer patients are over the age of 65 at the time of diagnosis, the utility of bevacizumab among elderly patients is not well defined. In subgroup analyses of older clinical trial participants, the addition of bevacizumab to platinum-based doublet chemotherapy did not provide a significant improvement in overall survival, but may be associated with an increased risk of treatment-related harms in older patients.[5,6] Furthermore, a recent observational study[7] also found no survival benefit with the use of bevacizumab among a cohort of Medicare beneficiaries within the Surveillance, Epidemiology, and End Results (SEER)-Medicare database.

Given the questionable utility of bevacizumab in the treatment of advanced NSCLC in elderly patients, additional research is warranted to better understand whether bevacizumab is a safe and effective therapy in this patient population. Although previous research has examined the safety and/or effectiveness of bevacizumab among older adults, these studies have important limitations. First, elderly clinical trial participants usually represent "fit" or healthy older adults rather than sicker elderly patients more commonly seen in a real-world clinical setting. Thus, treatment outcomes observed among elderly trial participants may not be generalizable to the larger population of older adults with advanced NSCLC. Second, little research has been done to evaluate associations between patient or health care system characteristics and the use, safety, or effectiveness of bevacizumab. In particular, previous research has not examined whether the use of bevacizumab differs among older patients based on age, race, socioeconomic status, or provider affiliation with provider-based cancer research networks such as the National Cancer Institute's (NCI) Community Clinical Oncology Program (CCOP). Third, the evaluation of the effectiveness of bevacizumab on survival among older patients has been largely restricted to patients receiving carboplatin-paclitaxel chemotherapy with or without bevacizumab. Although the FDA explicitly approved bevacizumab for use in combination

with carboplatin-paclitaxel chemotherapy, exclusion of other platinum-based chemotherapy regimens that are considered standard of care in advanced NSCLC may prohibit the complete capture of bevacizumab as a first-line treatment in the real-world setting. Last, although bevacizumab has been associated with an increased risk of severe bleeding including life-threatening or fatal pulmonary hemorrhage in clinical trials, research has not assessed the potential relationship between bevacizumab and severe treatment-related adverse events in the real-world setting.

This study utilizes a retrospective cohort design to examine the use, safety, and effectiveness of bevacizumab among a cohort of Medicare beneficiaries within the SEER-Medicare database who were diagnosed with advanced NSCLC and treated first-line with standard platinum-based doublet chemotherapy. It evaluates associations between the use of bevacizumab and clinical, sociodemographic, and health care system characteristics including age, race, socioeconomic status, and provider affiliation with the CCOP. Furthermore, this study evaluates the impact of bevacizumab on overall survival and hospitalization for severe treatment-related adverse events in order to better understand the utility of bevacizumab in the first-line treatment of older adults with advanced NSCLC.

1.2 Background

1.2.1 Lung Cancer in the United States

More than 200,000 new cases of lung cancer occur each year in the United States.[1] The probability of developing lung cancer increases with age and peaks at approximately 1 in 15 males and 1 in 22 females aged 70 years and older.[1] The overall age-adjusted incidence rate of lung cancer between 2002 and 2006 was 86.4 per 100,000 males and 55.5 per 100,000 females per year; however, the incidence rate for men has steadily declined while the incidence rate for women has gradually increased over the last twenty years.[1] The incidence rate of lung cancer also varies widely across the regions of the United States and is reflective of the differences in smoking prevalence among the

states; for example, during 2002 to 2006, the incidence rate of lung cancer exceeded 100 per 100,000 males in most Southern states whereas the incidence rate was less than 70 per 100,000 males in a majority of states in the West.[1]

Lung cancer leads to more than 150,000 deaths in the United States annually, representing approximately 28% of all cancer mortalities; each year more individuals die from lung cancer than from prostate, breast and colorectal cancer combined.[1] Traditionally, men have had higher mortality rates from lung cancer compared to women, but the gap has decreased considerably over the past two decades. The age-adjusted death rate for lung cancer in men in 2006 was 67.5 per 100,000 males, continuing its decline of 1% to 2% per year since its peak in 1990. The age-adjusted death rate for lung cancer in women on the other hand, has remained relatively constant since 1990 and was 40.2 per 100,000 females in 2006.[1]

Poor survival among lung cancer patients is due in large part to the high prevalence of advanced stage disease at the time patients are diagnosed; the five-year relative survival rate is less than 5% among patients diagnosed with advanced stage disease compared to a rate greater than 50% among patients diagnosed with localized stage lung cancer.[1] Unfortunately, detection of early stage lung cancer is difficult as symptoms typically do not manifest until after the disease has progressed. In addition, because lung cancer is most often present in smokers during their later years of life, symptoms can be difficult to distinguish from other lung complications brought about by smoking, such as emphysema and chronic obstructive pulmonary disease (COPD). When combined with the lack of acceptable and effective screening methods for lung cancer, the absence of discernible signs and symptoms contributes to a substantial proportion of advanced disease present at diagnosis.

As lung cancer progresses, symptoms may eventually become evident and can be quite distressful to patients. Tumor-induced changes in the lung, such as blocked airways and fluid accumulation in the chest cavity, can bring about symptoms and complications that may include shortness of breath, recurrent lung infection, hemoptysis and pain. These disease-related symptoms can significantly impact the health-related quality of life of patients by impairing functional ability,

causing psychological distress, and creating a substantial strain on family and social resources. Regrettably, because of the high prevalence of advanced disease present at diagnosis, treatment for many patients with lung cancer is palliative in nature and aims to prolong survival, reduce symptom burden, and maximize the quality of life.

Lung cancer is not only a physiologically debilitating disease, but it is also a tremendous financial burden to patients, their families, and society. Recent projections estimate that between 2010 and 2020, the United States will spend approximately $12 to $15 billion annually on lung cancer care.[8] Medical care costs for lung cancer are generally greatest during the initial stage of treatment and the last year of life because of the short time of survival. The annual cost of care for an individual lung cancer patient 65 years of age and older during initial treatment is estimated to be $60,000 (in 2010 dollars), whereas it will cost approximately $8,000 per year for patients continuing treatment and over $92,000 during the last year of life when the death is due to cancer.[8] By comparison, the costs of initial treatment for patients 65 years and older with colorectal, female breast or prostate cancer is approximately $52,000, $23,000, and $20,000, respectively. The cost of treatment during the last year of life for these patients when cancer is the cause of death is approximately $85,000 for colorectal cancer, $63,000 for female breast cancer, and $62,000 for prostate cancer.[8] In addition to the impact on direct medical care costs, lung cancer far surpasses other forms of cancer in the annual loss of time and economic productivity due to cancer-related illness and death; lung cancer contributed an estimated $39 billion in lost productivity in the United States among adults 20 years of age and older in 2010 compared to an estimated $13, $11, and $4 billion for colorectal, female breast, and prostate cancer, respectively.[9]

1.2.2 Population Differences in Lung Cancer

1.2.2.1 Differences by age

Lung cancer is a disease that generally affects older adults; nearly 70% of diagnoses occur in patients aged 65 years or older.[2] Furthermore, although the overall incidence of lung cancer in the United States decreased between 2000 and 2009, the incidence rate remained significantly higher in older adults and even increased among adults 75 years and older during this time period.[10] In addition, despite overall improvement in lung cancer mortality over the last few decades, survival remains poorest among individuals diagnosed at age 75 and older.[10]

Age differences in survival may be partly explained by age differences in the utilization of certain lung cancer treatments, such as chemotherapy and bevacizumab. Knowledge about the potential benefits and harms associated with various treatment options are generally derived from cancer clinical trials. However, older adults are often underrepresented in cancer clinical trials[11,12] limiting knowledge about the potential benefits and harms associated with various treatment options in these patients. In some cases older adults do not have the opportunity to take part in clinical trials due to restrictions on age, functional ability, and/or comorbidities among participants.[13,14] As a result, older adults who participate in clinical trials are more likely to be "fit" or healthy older patients. This is particularly concerning, as the overall health and performance status of patients within an age group can vary significantly and, thus, treatment outcomes among older trial participants may not be generalizable to sicker or more frail elderly patients. For example, older patients with good overall health may benefit from adjuvant chemotherapy, whereas older patients who are frail may have extreme difficulty tolerating such treatment and stand to gain little overall benefit from it.

The scarcity of information available to inform clinicians about the benefits and risks of therapies among both healthy and frail older adult patients can place significant uncertainty in the treatment decision process. Choosing to treat poorer functioning patients based on post-hoc analyses of healthier older adults may place sicker patients at unnecessary risk of treatment-related harm; not

treating poorer functioning patients based on the lack of safety and efficacy information may prevent patients from having a longer survival duration and/or better quality of life. Still, when evidence is available to support the use of certain treatments in select older lung cancer patients, chronological age remains a factor in determining whether patients receive guideline-recommended treatment; as a result, a significant proportion of older patients fail to receive more aggressive therapy from which they may benefit.[15]

1.2.2.2 Differences by race

Racial and ethnic disparities exist in the incidence, diagnosis, treatment, and outcomes associated with lung cancer in the U.S.[15-27] The burden of disease is disproportionately greater for blacks who are more likely to be diagnosed with and die from lung cancer. Black men in particular have the highest incidence rates of lung cancer among all racial, ethnic and gender groups; despite a steady decline since the mid-1980s, the incidence rate of lung cancer among black men in 2007 was 95.4 per 100,000 compared to a rate of 72.1 per 100,000 among white men.[2] Conversely, the difference in incidence rates among women has historically been much smaller. In 2007 the incidence rate of lung cancer among black women was 58.1 per 100,000 compared to a rate of 55.1 per 100,000 among white women.[2] Of note, the incidence rate of lung cancer among both men and women has traditionally been lowest among Hispanics who in 2007 had a combined incidence rate of 29.3 per 100,000.[2]

Historical differences in the prevalence of cigarette smoking have likely contributed to the disparities in lung cancer incidence between white and black Americans. An analysis[28] of the National Health Interview Survey (NHIS) from 1965 to 2008 showed that black males have been significantly more likely than white males to be smokers, but the difference in smoking prevalence has dramatically decreased over time. Black females were more also likely to be smokers than white females during the 1970s and 1980s, but that difference has been reversed. Other reasons behind

racial disparities in cancer incidence, although not entirely clear, are likely to include a combination of biological, environmental, and cultural influences including genetics, access to health care, and engagement in unhealthy behaviors that increase cancer risk.

Differences in the receipt of lung cancer treatment across racial and ethnic groups are well documented in previous studies of both early and late stage disease.[15,17-20,25,27] For example, in a recent study of patients with early-stage operable lung cancer, only 62 of 113 (55%) black patients chose surgery compared to 179 of 273 (66%) of white patients.[27] Similarly, additional studies found that blacks are less likely than whites to receive radiation or chemotherapy for advanced stages of lung cancer and are also less likely to receive appropriate treatment in a timely manner.[15,18,20]

Mortality from lung cancer remains highest among black patients, although the difference in lung cancer mortality between black and white patients has improved over the last two decades. Similar to observations in the incidence of lung cancer, the greatest difference in mortality rates is between black and white men; in 2007, the estimated mortality rate among black men was 82.7 per 100,000 compared to a rate of 64.9 per 100,000 among white men.[2] However, during the same time period, black women had a slightly lower mortality rate (39.2 per 100,000) compared to the rate among white women (41.1 per 100,000).[2] Higher incidence rates of lung cancer directly contribute to the increased mortality seen among black men. Still, the higher rate of mortality is also partly attributable to smaller proportions of blacks presenting with curable stages of disease. Between 2003 and 2007, only 12% of black males and 15% of black females presented with localized lung cancer compared to 15% of white males and 19% of white females.[2]

Underlying causes of the racial disparities seen in the treatment and mortality rates of lung cancer may be similar to those factors that contribute to disparities in the incidence of disease, particularly unequal access to and quality of care. Research has shown that when black patients receive treatment equal to that of non-black patients with similar prognoses, equal outcomes are observed.[29] Unfortunately, research has also shown that treatment of lung cancer across racial and ethnic groups is hardly equal.[15,18,20,25,27] Lower income and lack of insurance are significant

contributors to disparities in health care access and quality,[30] and because a significant proportion of blacks are poor and/or uninsured, they are less likely to have access to quality health care. In turn, we see the disproportionate rates of advanced disease at diagnosis, underutilization of available treatments, and worse survival outcomes in blacks as a result of poorer access to care. Thus, socioeconomic status is likely to be an important determinant of access to and receipt of appropriate and/or novel treatment for lung cancer and therefore may help to explain some of the racial differences observed in treatment utilization and outcomes among lung cancer patients. Finally, the unequal receipt of treatment among blacks may also be ascribed to differences in the rate of referral to oncologists, the availability of novel diagnostic technologies, poorer overall health, or the acceptance of treatment options by patients.[27,31-33]

1.2.2.3 Differences by socioeconomic status

Measures of socioeconomic status including education and income have been associated with lung cancer incidence,[34] treatment,[35,36] and survival outcomes.[35,37] Adults with less education, lower household income, and greater poverty have a higher incidence of lung cancer compared to adults with greater educational attainment (e.g., college), higher household income, and less poverty.[34] One probable explanation for the higher incidence of lung cancer among adults with lower socioeconomic status is an elevated rate of smoking in this population. Although differences in smoking prevalence have diminished over time, socioeconomic status still remains a significant predictor of smoking. A recent analysis[28] of the NHIS found that Americans who had less than a high school education, were unemployed, or lived below the poverty threshold were significantly more likely to be smokers compared to individuals who at least graduated high school, were in the work force or retired, or lived above the poverty threshold.

In addition to an increased incidence of lung cancer, socioeconomic status has also been associated with lower receipt of treatment[35,36] and higher mortality,[35,37] although evidence is

inconsistent. Still, recent research found that patients of lower socioeconomic status, such as those enrolled in an indigent health plan, are less likely to receive standard treatment compared to patients of higher socioeconomic status who are treated within the same single academic medical center.[35] Similarly, a separate study found that lung cancer patients residing in census tract areas of low median household income, high poverty, and low education attainment have poorer survival outcomes than patients living in census tract areas with higher median income, lower poverty, and greater education attainment, even when patients receive treatment within the same academic health care system.[37] However, these findings are contradicted by other research[38-40] results that suggest lung cancer outcomes do not differ based on the socioeconomic status of patients. Thus, it is not clearly understood if and to what extent an association exists between socioeconomic status measures and lung cancer mortality.

1.2.3 Provider-based Research Network Affiliation in Lung Cancer

Patient access to novel treatments for lung cancer and the quality of care they receive may be influenced by where and from whom care is provided; provider affiliations with academic medical centers and comprehensive provider-based cancer research networks, including the National Cancer Institute's (NCI) Community Clinical Oncology Program (CCOP) may promote earlier and more extensive use of new, advanced technology and interventions among patients. For example, previous research showed that lung cancer patients in the early to mid-1990s were more likely to be referred to an oncology specialist[31] or treated with chemotherapy for metastatic disease[41] if they received care from an academic medical center; the researchers proposed that diffusion of novel therapies into real-world practice is greater in settings such as academic medical centers where providers are more likely to be exposed to or involved in the development of such treatments.

Community-based physicians and provider groups not directly affiliated with large academic medical centers also have the opportunity to engage in the early use and development of novel

therapies through provider-based research networks like the CCOP. The CCOP assists in the dissemination and implementation of novel cancer care advancements through a research infrastructure that connects community-based physicians and provider groups with principal investigators and academic medical institutions.[42,43] Community-based providers and provider groups participating in the CCOP gain access to clinical trials and research results concerning novel therapies and technological advancements that may not otherwise be accessible outside of the research network.[43] An important motivating factor for participation, providers perceive involvement in the CCOP enables them to deliver higher quality of care to their patients by keeping them updated on state-of-the-art treatment.[44] Indeed, research findings support that community-based physician participation in provider-based research networks results in increased patient accrual into clinical trials and enhanced adoption of novel cancer care, ultimately characterizing an effective translation between research and clinical practice.[45-48]

1.2.4 Advanced Non-Small Cell Lung Cancer

Lung cancer is divided into two major types based on microscopic evaluation of the size and appearance of malignant cells: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Small cell lung cancer is strongly associated with smoking and is considered to be the more aggressive form of lung cancer, with greater potential for metastasis. SCLC comprises nearly 13% of newly diagnosed lung cancers[49] and patients typically present with distant spread of disease at diagnosis resulting in poor prognosis and survival.[50] Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 80% to 85% of all cases and includes adenocarcinoma, squamous cell, large cell, and not otherwise specified (NOS) histologies. Smoking is the greatest risk factor for the development of NSCLC, and a majority of patients have locally advanced or metastatic disease at the time they are diagnosed.[51]

Prognostic factors such as stage at diagnosis and the performance status (PS) of the patient can be predictive of survival in patients with NSCLC. Performance status of the patient is commonly measured using the Eastern Cooperative Oncology Group Performance Status scale (ECOG) which grades the functional ability of the patient and helps to determine whether patients are likely to tolerate and benefit from certain treatments, such as chemotherapy.[52] Patients are graded on a scale of 0 to 4, with 0 indicating that the patient is fully active and able to physically perform without restriction and 4 indicating that the patient is completely disabled and incapable of ambulation or self-care. Prognostic factors that indicate improved survival in NSCLC include early stage at diagnosis, good performance status (Eastern Cooperative Oncology Group 0 or 1), less than 5% weight loss from baseline, and female gender.[53] Age and histology subtype of NSCLC do not appear to significantly influence prognosis. However, histology can influence treatment choice and biomarkers such as the epidermal growth factor receptor (EGFR) and the k-ras oncogene may have important predictive value for treatment response and/or prognosis and survival.[54]

Platinum-based doublet chemotherapy containing either carboplatin or cisplatin is considered the standard treatment option for most patients with advanced stage NSCLC. Platinum-based doublet regimens lessen cancer-related symptoms, prolong survival, and improve quality of life.[55] However, the survival benefit of standard chemotherapy remains poor. Median time to tumor progression with platinum-based chemotherapy is approximately 4-5 months while median overall survival duration is approximately 8-11 months; further, 1-year survival with standard treatment is less than 50% and 2-year survival is less than 20%.[3,4] Scientific and clinical progression in understanding the pathogenesis of cancerous tumors as well as the need to improve upon the survival benefits of standard platinum-based chemotherapy in the treatment of advanced NSCLC guided the development of novel, targeted therapies, including bevacizumab.

1.2.5 Bevacizumab in Advanced Non-Small Cell Lung Cancer

Bevacizumab, a humanized monoclonal antibody that inhibits angiogenesis and tumor growth by targeting the vascular endothelial growth factor (VEGF) in tumors, is currently the only monoclonal antibody approved by the FDA for the first-line treatment of advanced NSCLC. Based on improvements in response rate, progression-free survival, and overall survival during clinical trials, bevacizumab is specifically approved for use in combination with carboplatin-paclitaxel chemotherapy as first-line treatment of patients with advanced stage non-squamous NSCLC;[56,57] use of bevacizumab is restricted to patients with non-squamous histology due to a prohibitive rate of life-threatening or fatal pulmonary hemorrhage in patients with squamous histology tumors.[57]

Knowledge about the efficacy and safety of bevacizumab in treating advanced NSCLC is largely based on the results of several clinical trials. However, information about the use of bevacizumab and its potential benefits or safety concerns among specific subpopulations of interest including older adults, racial minority patients, and patients of lower socioeconomic status is limited. Subgroup analyses[5,6] of older clinical trial participants have found that the addition of bevacizumab to platinum-based doublet chemotherapy improves progression-free survival among older adults, but does not appear to significantly improve overall survival; in addition, the use of bevacizumab may increase the risk of treatment-related harms among older patients, although this potential association remains questionable as subgroup analyses yielded conflicting results. However, results of subgroup analyses must be interpreted cautiously as older clinical trial participants are typically "fit" or otherwise healthy individuals with greater functional ability than sicker or frailer elderly adults; treatment outcomes among older trial participants may not be representative of expected outcomes in the general population of older adults with advanced NSCLC. Nevertheless, findings from a recent observational study[7]also suggest that the addition of bevacizumab to carboplatin-paclitaxel chemotherapy is ineffective in improving overall survival among Medicare beneficiaries with advanced NSCLC treated in the real-world setting.

Although subgroup analyses of older clinical trial participants and an observational study of Medicare beneficiaries provide some level of knowledge about the safety and effectiveness of bevacizumab among older adults with advanced NSCLC, there is a significant absence of information on whether treatment outcomes with bevacizumab vary across racial or socioeconomic groups. For example, overall survival results among ECOG 4599 clinical trial participants receiving carboplatin-paclitaxel with or without bevacizumab suggest that both white and black participants benefit from the use of bevacizumab; however, as blacks only made up approximately 5% of the total clinical trial sample, their underrepresentation significantly limited any comparison of treatment effectiveness between racial groups.[56] Similarly, the infrequent inclusion of socioeconomic measures in clinical trials and the scarcity of observational studies on bevacizumab in NSCLC contribute to the absence of information on the potential associations between bevacizumab outcomes and socioeconomic status.

1.3 Significance

Lung cancer is a significant burden to public health in the United States, particularly among older adults who make up the majority of annual lung cancer diagnoses. Older adults typically present with advanced stage disease, are less likely to receive definitive treatment, and have poorer survival outcomes compared to younger patients. Similarly, blacks are also disproportionately affected by lung cancer. Blacks are more likely to develop lung cancer, present with advanced stages of disease, and die from lung cancer compared to members of all other races and ethnicities in the US. Furthermore, although research indicates that equal outcomes are observed when treatment of lung cancer is similar across various racial and ethnic groups,[17,19,24,29,58-64] racial disparities in the receipt of lung cancer treatment and subsequent outcomes continue to exist. In addition, although evidence is significantly limited, socioeconomically disadvantaged patients are less likely to receive standard care[35] and have poorer survival outcomes[35,37] than patients of higher socioeconomic status. Lastly, participation in provider-based research networks such as the CCOP has been associated with provider adoption of

novel therapies and greater utilization of these state-of-the-art treatments among community-treated patients.[45-48] Together these research findings suggest that patient and health system characteristics are important determinants of patient access to, receipt of, and benefits from available treatments.

Bevacizumab, a novel targeted therapy used in combination with standard platinum-based doublet chemotherapy, provides an additional treatment option for select patients with advanced NSCLC. However, the effectiveness and safety of bevacizumab in the treatment of advanced non-small cell lung cancer in the broader population of patients is limited, especially among older adults and patients of racial minority and lower socioeconomic backgrounds. Results from a recent observational study concur with subgroup analyses of older clinical trial participants suggesting that the addition of bevacizumab to platinum-based chemotherapy does not yield a significant overall survival benefit in older patients. Nevertheless, this observational study restricted its analysis of bevacizumab to older patients specifically treated with carboplatin-paclitaxel chemotherapy. Including older patients treated with other platinum-based chemotherapy regimens that are standard of care in advanced NSCLC would allow for more complete capture of the utilization of bevacizumab. In turn, greater capture of bevacizumab utilization may permit the assessment and increased understanding of the safety and effectiveness of bevacizumab in a broader population of older patients with advanced NSCLC, including patients of different racial and socioeconomic backgrounds.

Given that previous research has identified disparities in the receipt of traditional lung cancer treatments among older adults, patients of minority race, and socioeconomically disadvantaged patients, it is important to understand if the same differences exist in the use of newer therapies such as bevacizumab. In addition, it is imperative to determine whether bevacizumab is beneficial when administered to older patients in the larger NSCLC population. Recognition of patient and health system characteristics associated with the utilization, safety, and effectiveness of bevacizumab will help clinicians, policy makers, and other researchers improve dissemination of information, patient-provider communication about treatment decisions, and increase access to novel therapies for all

cancer patients in order to minimize differences in treatment utilization and outcomes. Therefore, the overall objectives of this study are to identify patient and health system characteristics associated with the use of bevacizumab and to evaluate the effectiveness and safety of bevacizumab in older patients with advanced NSCLC.

To address the objectives of this study, we used the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database available through a collaborative effort between the National Cancer Institute (NCI) and the Centers for Medicare and Medicaid Services (CMS). Briefly, the SEER Program of the NCI is a coordinated system of 17 distinct population-based cancer registries strategically distributed throughout the United States to represent approximately 28 percent of the US population and is the only comprehensive population-based source in the country that contains data on stage at diagnosis and patient survival. SEER registries collect data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. For eligible patients enrolled in fee-for-service coverage for Medicare Parts A and B, all Medicare claims for covered healthcare services provided during patient Medicare eligibility are linked to SEER data. For our study, we used SEER-Medicare data that included all locally advanced and metastatic non-small cell lung cancer cases diagnosed between January 1, 2004 and December 31, 2007 as well as all Medicare fee-for-service claims for each patient starting 12 months prior to the date of diagnosis (as early as January 1, 2003) through the end of 2009.

1.4 Specific Aims and Hypotheses

Assessing the utilization of bevacizumab and the resultant treatment effects among older adults with advanced non-small cell lung cancer will provide crucial evidence regarding potential sociodemographic differences in the use of novel cancer treatments as well as the utility of bevacizumab in treating older adults with advanced non-small cell lung cancer. These important issues will be addressed by the following research aims:

Aim 1: To describe the utilization of bevacizumab in combination with standard platinum-based doublet chemotherapy as first line treatment for older adults with advanced non-small cell lung cancer and to identify the clinical, sociodemographic, and health system factors associated with its use.

Bevacizumab is a monoclonal antibody approved in the United States in combination with carboplatin and paclitaxel chemotherapy for the first-line treatment of patients with unresectable, locally advanced or metastatic nonsquamous non-small cell lung cancer. The following hypotheses will be tested in Aim 1:

H1: Among older adults with a primary diagnosis of advanced nonsquamous non-small cell lung cancer, non-white patients are significantly less likely than white patients to receive bevacizumab in combination with standard platinum-based doublet chemotherapy.

H2: Among older adults with advanced non-small cell lung cancer, patients of lower socioeconomic status are significantly less likely than patients of higher socioeconomic status to receive bevacizumab in combination with standard platinum-based doublet chemotherapy.

H3: Among older adults with advanced non-small cell lung cancer, patients 70 years or older are significantly less likely than patients 66 to 69 years of age to receive bevacizumab in combination with standard platinum-based doublet chemotherapy.

H4: Among older adults with advanced non-small cell lung cancer, patients who receive treatment from a provider affiliated with the National Cancer Institute (NCI) Community Clinical Oncology Program (CCOP) are significantly more likely to receive bevacizumab in combination with standard platinum-based doublet chemotherapy compared to patients who receive treatment from non-CCOP-affiliated providers.

Aim 2: To determine whether the use of bevacizumab in combination with standard platinum-based doublet chemotherapy as first-line treatment of older adults with advanced

non-small cell lung cancer is associated with a benefit of improved overall survival.

The following hypothesis will be tested under Aim 2:

H5: Among older adults with advanced non-small cell lung cancer, patients who receive bevacizumab in combination with standard platinum-based doublet chemotherapy as first line treatment do not have significantly improved overall survival compared to patients receiving standard platinum-based doublet chemotherapy only.

Aim 3: To determine whether the use of bevacizumab in combination with standard platinum-based doublet chemotherapy as first-line treatment of older adults with advanced non-small cell lung cancer is associated with an increase in hospitalizations for severe treatment-related adverse events.

The following hypothesis will be tested under Aim 3:

H6: Among older adults with advanced non-small cell lung cancer, patients who receive bevacizumab in combination with standard platinum-based doublet chemotherapy as first line treatment have a significantly greater incidence of severe adverse events (i.e., neutropenia, gastrointestinal perforation, or severe hemorrhage) resulting in hospitalization compared to patients receiving standard platinum-based doublet chemotherapy only.

1.5 Summary

Lung cancer primarily occurs among older adults over the age of 65 and the majority of patients with newly diagnosed non-small cell lung cancer present with advanced stage disease. Although there is no cure, platinum-based doublet chemotherapy is the standard of treatment for patients with advanced stage disease and has been shown to improve both survival and quality of life.[55] The addition of bevacizumab to platinum-based double agent chemotherapy has further improved response to treatment and overall survival in advanced non-small cell lung cancer

patients.[65] However, retrospective subgroup analyses[5,6] of elderly trial participants and results of a recent observational study[7] of Medicare beneficiaries found no overall survival benefit with the addition of bevacizumab to platinum-based doublet chemotherapy, suggesting that bevacizumab may not be effective in prolonging survival among older patients. Furthermore, knowledge about the benefits and harms of adding bevacizumab to standard platinum-based chemotherapy among minority or socioeconomically disadvantaged patients is limited as minority patients are often underrepresented in clinical trials; this is particularly concerning as lung cancer incidence and mortality is disproportionately higher among blacks. Clearly additional research is needed to delineate whether the utilization of bevacizumab in combination with standard platinum-based doublet chemotherapy differs by age, race, socioeconomic status, or health system factors such as provider affiliation with community-based research networks. In addition, further research within a broader population of older patients is essential to verify previous associations between bevacizumab and overall survival and to determine if this association differs across age, race, or socioeconomic groups. Lastly, an assessment of the relationship between the use of bevacizumab and hospitalization for severe adverse events is needed; determining whether any potential association differs by age, race, or socioeconomic status would provide valuable information about the safety of bevacizumab and identification of patients who may be at greater risk for harms with its use.

This study evaluated the utilization, safety, and effectiveness of bevacizumab among older adults with advanced non-small cell lung cancer using SEER-Medicare data for incident cases diagnosed between 2004 and 2007. In particular, the study assessed whether the use of bevacizumab varied according to chronological age, race, socioeconomic status, or provider affiliation with the CCOP, a provider-based research network. Detection of differences in the use of bevacizumab across age, race, socioeconomic status, or provider affiliation with the CCOP in this study will support the need for future research to identify why variations exist. Chronological age as a determinant of bevacizumab use independent of relevant clinical factors may result due to the scarcity of information available to clinicians to make sound risk-benefit assessments and treatment decisions with older

patients. Physician bias toward older adults or patient willingness to accept treatment may also influence the use of bevacizumab among older adults. Similarly, physician and patient characteristics may explain differences in the use of bevacizumab across racial groups. Understanding reasons behind age, race, and socioeconomic differences in the use of bevacizumab will in turn help to guide future policy development. For example, identifying generational, cultural and linguistic barriers between patients and physicians can assist in developing policies to improve cultural competence among clinicians, patient-provider communication strategies, and informational resources available to patients. Furthermore, association between the use of bevacizumab and provider affiliation with the CCOP may better inform clinicians and policymakers as to the effectiveness of provider-based research networks in rapidly disseminating clinical trial information into the community setting as well as promoting the quick diffusion of novel, evidence-based treatments into community practice.

Identification of significantly improved overall survival and similar incidence rates of hospitalization for severe adverse event outcomes with the addition of bevacizumab to standard platinum-based doublet chemotherapy will demonstrate the utility of bevacizumab among older adults and will also have important research and policy implications. For example, future research may be warranted to delineate clinical or genetic characteristics of older patients to help understand why survival or adverse event outcomes differ. Also, recognition of age differences in survival or adverse event outcomes associated with bevacizumab will encourage the development of policies to improve the availability and completeness of clinical information for treatment decision making. For example, better recruitment and inclusion of older adults and minority patients in clinical trials of novel cancer therapies along with improvements in the speed, breadth, and efficiency at which trial results are disseminated may enhance the ability and confidence of physicians in communicating treatment options with patients and making sound clinical decisions.

CHAPTER TWO

LITERATURE REVIEW

2.1 Non-Small Cell Lung Cancer: Disease and Management

2.1.1 Risk Factors of Non-Small Cell Lung Cancer

A number of lifestyle and environmental risk factors contribute to the incidence of lung cancer. However, smoking is clearly the single most important risk factor for the development of lung cancer and is responsible for approximately 90% of lung cancer cases in the United States. Smoking leads to the development of lung cancer by producing mutations in tumor suppressor genes and dominant oncogenes and by impairing mucociliary clearance in the lungs and inhibiting the responsiveness of the immune system.[66] The risk of lung cancer for current smokers is approximately 10 to 20 times the risk of lung cancer for persons who have never smoked.[67] In addition, the risk of developing lung cancer among smokers increases with the number of cigarettes and the duration of smoking. Conversely, quitting smoking gradually reduces the risk of developing lung cancer up to the point where the risk remains about twice that of someone who never smoked.[68]

Researchers have estimated that up to 60% of patients are current smokers at the time of diagnosis and over 80% of them continue to smoke following the detection of lung cancer.[69] These estimates are concerning considering that continued smoking has been associated with an increased risk of developing second primary lung cancer and an increased risk of dying.[70,71] Furthermore, research suggests that continued smoking following the diagnosis of cancer may impair the effectiveness and/or worsen the adverse effects of treatment.[72,73] On the other hand, lung cancer

patients who quit smoking after their diagnosis have improved oxygenation and immune response, increased fatigue and shortness of breath, and improved performance status, appetite, and mood.[74-76] In addition to improving the quality of life for patients, smoking cessation has been associated with increased survival time.[71,77] Thus, successful smoking cessation is a critical component in reducing the risk of lung cancer among smokers and in maximizing survival and the quality of life in lung cancer patients.

Although smoking is the predominant risk factor in most cases, lung cancer is still a significant health concern among individuals who have never smoked.[78] Lung cancer in persons who have never smoked appears to occur more often in women compared to men, particularly in Asia where as much as 80 percent of women with lung cancer are never smokers compared to only 10 to 15 percent of men.[79,80] In contrast, Wakelee et al. estimated that 19 percent of women with lung cancer in the United States are never smokers versus just 9 percent of men.[79] Thus, although the evidence is not as well established, it is apparent that a number of risk factors other than smoking contribute to the development of lung cancer in a noticeable proportion of patients. Of these other risk factors, those more commonly associated with lung cancer include the environmental toxins second-hand smoke, asbestos, and radon gas.[67] In addition, individuals with pulmonary fibrosis, HIV infection, a family history of lung cancer or specific genetic markers may also be at an increased risk of developing lung cancer, particularly if they are also smokers.[81-84] Still, the extent to which these other risk factors contribute to the development of lung cancer either in addition to or independent of smoking needs to be clarified.

2.1.2 Symptoms of Non-Small Cell Lung Cancer

Early detection of lung cancer is difficult as pulmonary tumors are often asymptomatic during early stages of development.[85] Detection of early stage disease is also challenged by the lack of an effective screening method that has been shown to significantly reduce mortality from lung cancer.

Furthermore, signs of lung cancer are similar to those of other respiratory diseases common to smokers including chronic obstructive pulmonary disease (COPD) and pneumonia. For example, both lung cancer and COPD may involve symptoms related to respiratory distress, such as cough and hemoptysis, as well as non-specific symptoms, such as fatigue and weight loss. Thus, even if symptoms of lung cancer are present at an early stage of disease, they may be difficult to distinguish from complications of other respiratory diseases, particularly if lung cancer is not suspected to begin with. In addition, there is often a delay between the time when symptoms first present and the time when patients seek out medical care and receive treatment from a physician, further decreasing the likelihood of discovering lung cancer at an early stage of development.[86,87]

The symptoms present at diagnosis may include symptoms related to the primary tumor in the lung as well as non-specific symptoms that indicate the tumor has spread beyond the pulmonary cavity.[88] Common symptoms include those related to the primary tumor and respiratory distress such as cough, difficulty breathing, chest pain, and hemoptysis.[85,88] Cough is the most common symptom of lung cancer and often occurs along with difficulty breathing and increasing amounts of sputum that may even contain traces of blood; although hemoptysis is also common, it is rarely severe in lung cancer and therefore may not always be a tell-tale sign of malignancy.[88] In patients with COPD, difficulty resolving acute exacerbations of the disease may also signify the presence of a tumor.[88]

Other respiratory related symptoms may occur as a result of the cancer extending within the chest area. Intrathoracic spread of a tumor may lead to: laryngeal nerve damage resulting in hoarseness, poor expectoration, and increased risk of aspiration; persistent and dull chest pain unrelated to coughing or breathing; and the buildup of fluid around the lungs that leads to shortness of breath.[88] Furthermore, the spread of lung cancer to common sites of distant metastases including the bones, liver and brain can result in the presence of non-specific systemic symptoms such as bone pain, weakness, fatigue, anorexia, weight loss, headache, confusion, and nausea and vomiting.[88]

Given the apparent association of constitutional symptoms with advanced stages of disease, previous research has examined the relationship between the types of symptoms present during

examination and prognosis.[89,90] Prognosis was poorest among patients with non-specific systemic symptoms such as weight loss and fatigue or symptoms attributable to metastases such as bone pain. Furthermore, within each tumor stage, the presence of systemic symptoms was associated with a declining prognosis, suggesting the presence of extensive disease.[88] Conversely, prognosis was most favorable among patients who were asymptomatic or presented with symptoms related to the primary tumor only. Additional research further confirmed the association between non-specific symptoms and advanced disease by finding that abnormal clinical presentations were associated with evidence of metastatic disease upon radiographic evaluation and CT scans; patients without non-specific systemic symptoms at presentation were highly unlikely to have metastases detected.[91] As a result of these findings, it has since been recommended that patients with known or suspected lung cancer receive timely and efficient care that includes a thorough medical history, physical examination, and standard laboratory tests in order to effectively identify patients with a greater likelihood of metastatic disease.[88]

2.1.3 Diagnosis and Staging of Non-Small Cell Lung Cancer

Diagnosis of non-small cell lung cancer in a patient suspected of having the disease is dependent on a complete detailed history and examination of the patient that serves to identify signs and symptoms associated with extensive or metastatic disease, significant comorbid conditions, and assess pulmonary and overall health status. These assessments, in turn, help determine what course of therapy is likely to be most effective and tolerated by the patient. In addition to a complete history and physical examination, common tests performed to assist in the diagnosis and staging of non-small cell lung cancer include laboratory tests, radiographic imaging, and tissue sampling. Laboratory tests are conducted to identify abnormalities that may suggest the presence of advanced or metastatic disease such as elevated liver enzymes, calcium, alkaline phosphatase, and anemia. Contrast-enhanced computed tomography (CT) is useful for staging as it can illustrate the size of a tumor and

where it is located in relationship to the chest wall and other mediastinal structures; CT can also identify lymph nodes and other lesions that suggest metastasis. Additional imaging methods such as positron emission tomography (PET) and contrast-enhanced magnetic resonance imaging (MRI) may also be used to further evaluate and detect suspected malignant tumors and metastases. Further, abnormal imaging findings are then followed up and confirmed with histopathologic results from tissue samples of the primary tumor or lymph nodes that can be obtained by needle aspiration, biopsy or surgical procedures; noninvasive techniques alone are not enough to confirm a diagnosis or accurately determine the stage of the disease.[92]

Staging of non-small cell lung cancer is essential in determining the prognosis and appropriate course of treatment and can be divided into two components, clinical staging and pathologic staging. Clinical staging is done initially and occurs following the completion of the medical history, physical examination, laboratory testing, imaging, and tissue sampling. Pathologic staging combines clinical staging information with histopathologic data collected during pathologist evaluation of a resected tumor; in some cases, the determined stage of the cancer changes following pathologic evaluation which can then alter the prognosis and course of treatment. Both clinical and pathologic staging are based upon the tumor node metastasis (TNM) staging system for non-small cell lung cancer (NSCLC). The TNM staging system grades the characteristics of the primary tumor such as size (T), involvement of regional or distant lymph nodes (N), and the presence or absence of distant metastasis (M). The combination of the T, N, and M grades determine the overall disease stage that is then used to determine prognosis and assist in deciding the appropriate treatment options.[92] Since the 7the edition of the TNM staging system recently went into effect in January of 2010, the 6th edition will be used for this study.

2.1.4 Treatment of Advanced Non-Small Cell Lung Cancer

2.1.4.1 Evaluation of performance status and the comprehensive geriatric assessment

The prognosis and management of non-small cell lung cancer are largely dependent on the stage of disease at the time of diagnosis. However, the performance status (PS) of the patient and the presence of other comorbid conditions can have an important influence on the selection of treatment and the projected outcome of the disease. As may be expected, patients with poor performance status and significant weight loss often have shortened survival.[93,94] Furthermore, older adults are more likely than younger patients to have comorbid conditions and age associated physiologic changes that can contribute to greater frailty, poorer performance status, and limit the tolerability and benefits of aggressive treatment. However, given the large heterogeneity in comorbid conditions and performance status among patients of the same age, chronologic age alone is not enough to determine whether a patient will benefit or tolerate a specific treatment. As a result, clinicians have developed the comprehensive geriatric assessment (CGA) to use as part of the baseline evaluation of older adults with cancer. The CGA, in addition to providing a more comprehensive appraisal of the functional status of older patients,[95] evaluates cognitive functioning, nutrition, comorbidity, mental well-being, and social support. Each component of the CGA provides additional information that can be used to identify potential complications of treatment, predict survival, improve mental health, and effectively manage pain in older patients.[96] Furthermore, recent studies have shown that the utilization of a brief, self-administered questionnaire consisting of the measures of geriatric assessment is feasible, well accepted by patients, and reliable in both clinical practice and clinical trial settings.[97,98]

2.1.4.2 Surgery

Although surgical resection provides the best chance for long-term survival and is the standard of care for patients with stage I and II non-small cell lung cancer,[99] surgical resection is

rarely indicated for advanced stages of disease. However, other surgical procedures may be performed among patients who have stage IIIB tumors with pleural effusion and among certain patients with solitary brain metastases.

Among patients with pleural effusion, fluid collects in the pleural space between the lungs and chest wall, prohibiting the lungs from fully expanding and leading to shortness of breath. To remove the fluid from the pleural cavity and relieve related symptoms, a physician may perform one or more of the following options: thoracentesis, tunneled catheter placement, or pleurodesis. Thoracentesis is the simplest method to treat pleural effusion, and involves the insertion of a small catheter into the pleural space to allow the fluid to drain out.[100] For patients who experience rapid fluid accumulation following thoracentesis, more aggressive measures may be necessary, including the placement of a tunneled catheter or pleurodesis. The tunneled catheter is similar to thoracentesis except that the catheter is left in the pleural space and connected to a container and hand pump, allowing fluid accumulation to be managed on a daily basis.[100] Pleurodesis is a more invasive treatment option in which a chemical irritant (e.g., talcum powder) is placed into the pleural space following fluid drainage; the membranes lining the lungs and chest wall become inflamed and attach to one another, closing off the pleural space and thereby preventing further fluid accumulation.

Brain metastases are associated with poor prognosis and quality of life and appear within one year of diagnosis in up to half of all patients with non-small cell lung cancer.[101] Among patients with a solitary brain metastasis, surgical removal is the standard of care and has been shown to prolong survival and prevent recurrent metastases in the brain.[102,103] However, only 14-44% of brain metastases are resectable[104] and there is no evidence to support the use of surgery among patients with multiple brain metastases.[105] Instead, two distinct radiation treatments are commonly used to manage multiple or unresectable brain metastases and these methods are described below.

2.1.4.3 Radiation therapy

Radiation therapy (RT) may be used in advanced non-small cell lung cancer to treat brain metastases and also to manage symptoms in the palliative care setting. Two distinct radiation therapies, whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS), have been used in the treatment of brain metastases. When these therapies are used alone, median survival may be prolonged 3-5 months with WBRT[106] and approximately 9 months with SRS.[107] However, when WBRT is combined with SRS, control of brain disease is significantly improved and survival can be prolonged up to 11 months.[108] Still, recent concerns that WBRT may significantly impair learning and memory function[109] may lead to greater use of SRS as a single modality, particularly if neurocognitive function can be maintained and survival rates comparable to combined treatment can be achieved.[104]

In patients with stage IV NSCLC, radiation therapy can also be used to manage symptoms brought about by localized and distant metastatic disease (e.g., dyspnea, hemoptysis, and bone pain).[110] However, the duration and dose of RT to be used in the palliative setting is unclear and may be dependent on the performance status and prognosis of the patient. For example, a recent review found that both higher and lower doses of RT were effective in reducing symptoms, but higher doses were associated with significant increases in both survival and toxicity.[111] Furthermore, stereotactic body radiation therapy that delivers high doses of radiation to a precise target in the body may be useful in the palliative care setting, particularly among older adults who otherwise may not receive or tolerate standard radiation therapy.[112]

2.1.4.4 Chemotherapy

The American Society of Clinical Oncology (ASCO) guideline[55] recommends the use of first-line chemotherapy among patients with advanced non-small cell lung cancer (stage IIIB with pleural

effusion and stage IV) and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, and possibly 2. A meta-anlysis[113] that evaluated the benefit of adding another cytotoxic agent to a single- or double-agent chemotherapy regimen found that the use of two cytotoxic drugs as first-line treatment significantly improves overall survival and is preferred over the use of a single cytotoxic agent.[55] However, because the addition of a third cytotoxic agent does not provide further survival benefit beyond the use of double-agent chemotherapy and is associated with significantly greater toxicity,[113-116] the concurrent use of three cytotoxic drugs is not recommended.[55]

Chemotherapy combinations that may be used to treat advanced non-small cell lung cancer are included in Table 2.1. Generally, chemotherapy combinations are divided into platinum-based and non-platinum combinations. Current platinum-based doublet regimens typically include the use of cisplatin or carboplatin along with one of the following "third-generation" agents: paclitaxel, gemcitabine, docetaxel, vinorelbine, irinotecan or pemetrexed. In addition, common non-platinum regimens that may be used include gemcitabine plus docetaxel, paclitaxel, pemetrexed or vinorelbine and paclitaxel plus vinorelbine. Regimens may vary by administration frequency and schedule, but current recommendations for the duration of treatment suggest that no more than six cycles of any double-agent chemotherapy should be administered.[55] The administration of first-line treatment beyond four to six cycles provides no overall survival advantage and may increase the risk for toxic effects.[117-120]

Table 2.1 Chemotherapy regimens used for advanced non-small cell lung cancer

Platinum-based regimen	Possible administration schedule and frequency[a]
Carboplatin (or cisplatin) & paclitaxel	Platinum agent & paclitaxel: Administer on Day 1; Repeat every 3 weeks (21 days) for max of 6 cycles
Carboplatin (or cisplatin) & docetaxel	Platinum agent & docetaxel: Administer on Day 1; Repeat every 3 weeks (21 days) for max of 6 cycles

Table 2.1 (continued)

Carboplatin (or cisplatin) & pemetrexed	Platinum agent & pemetrexed: Administer on Day 1; Repeat every 3 weeks (21 days) for max of 6 cycles
Carboplatin (or cisplatin) & gemcitabine	Platinum agent: Administer on Day 1; Gemcitabine: Administer on Days 1 and 8; Repeat every 3 weeks (21 days) for max of 6 cycles
Carboplatin (or cisplatin) & vinorelbine	Platinum agent: Administer on Day 1; Vinorelbine: Administer on Days 1 and 8; Repeat every 3 weeks (21 days) for max of 6 cycles
Non-platinum-based regimen	
Gemcitabine & paclitaxel	Gemcitabine: Administer on Days 1 and 8; Paclitaxel: Administer on Day 8; Repeat every 3 weeks (21 days) for max 6 cycles
Gemcitabine & docetaxel	Gemcitabine: Administer on Days 1 and 8; Docetaxel: Administer on Day 8; Repeat every 3 weeks (21 days) for max 6 cycles
Gemcitabine & pemetrexed	Gemcitabine: Administer on Days 1 and 8; Pemetrexed: Administer on Day 8; Repeat every 3 weeks (21 days) for max 6 cycles
Gemcitabine & vinorelbine	Gemcitabine/vinorelbine: Administer on Days 1 and 8; Repeat every 3 weeks (21 days) for max 6 cycles
Paclitaxel & vinorelbine	Paclitaxel/vinorelbine: Administer on Day 1; Repeat every 2 weeks (14 days) for max 9 cycles

[a]The dosing schedules and frequencies presented in the table represent those that have been used in phase III randomized trials of each regimen. Actual schedules and frequencies used in clinically practice may differ from those described in the table.

Although multiple chemotherapy combinations are beneficial in advanced non-small cell lung cancer, platinum-based regimens with cisplatin or carboplatin are preferred based on better response rates and prolonged overall survival compared to non-platinum-based regimens.[55] However, no one single platinum-based regimen stands out as the superior treatment option in advanced non-small cell lung cancer.[55] In addition, there is little convincing evidence to support the use of either platinum agent (carboplatin or cisplatin) over the other. A meta-analysis[121] of nine randomized trials comparing carboplatin- to cisplatin-based regimens found that patients treated with carboplatin had a lower

response rate (24% vs. 30%), slight increase in hazard of mortality (hazard ratio [HR] = 1.07; 95% CI 0.99-1.15), and greater thrombocytopenia (12% vs. 6%; OR = 2.27; 95% CI 1.71-3.01) compared to patients treated with cisplatin. However, patients who received carboplatin were less likely to have nausea and vomiting (8% vs. 18%; OR = .42; 95% CI 0.33-0.53) or nephrotoxic effects (0.5% vs. 1.5%; OR = 0.37; 95% CI 0.15-0.88) compared to patients who received cisplatin. Thus, when making treatment decisions between carboplatin and cisplatin, physicians and patients may consider the potential tradeoff between efficacy and adverse effects. Given the relatively small survival benefit and lower tolerability profile of cisplatin, carboplatin may be used more often in advanced stage non-small cell lung cancer where the intent of treatment is to manage symptoms and maximize quality of life.[122]

Furthermore, the small improvements in survival seen with regimens that utilize either of the platinum agents may not outweigh increases in toxicity for some patients. For example, a meta-analysis comparing platinum-based and non-platinum regimens found a slight improvement in 1-year survival (34% vs. 29%) as well as significantly greater hematologic toxicity, nephrotoxicity, and gastrointestinal complications with the use of platinum-based chemotherapy.[123] Therefore, non-platinum chemotherapy regimens may be appropriate alternatives for patients who may not tolerate or have contraindications (e.g., poor renal function or allergy to platinum agents) to platinum-based treatment.

The appropriate use of chemotherapy in elderly patients and patients with a PS of 2 is not well delineated. Some elderly patients and patients with a PS of 2 may have difficulty tolerating either platinum-based or non-platinum double-agent chemotherapy regimens. In addition, the concern for greater toxicity and the exclusion or underrepresentation of these patients from randomized trials has inhibited our ability to reveal the benefit of combination therapy among elderly patients and patients with a PS of 2 to some degree. Furthermore, comparisons of double-agent and single-agent regimens in elderly patients and patients with a PS of 2 have found mixed results; two trials[124,125] did not find any additional benefit in overall survival with double-agent therapy among

elderly patients and patients with a PS of 2, while another trial[126] found that the survival benefit from combination therapy was similar between older and younger patients. Given the previous lack of consistent evidence, data from trials supported the use of single-agent chemotherapy for elderly patients and patients with a PS of 2, but was insufficient to recommend for or against the use of double-agent chemotherapy.[55] Subgroup analyses of several additional trials[127] have shown that fit elderly patients are able to tolerate and benefit from platinum-based and non-platinum doublet chemotherapy regimens. In addition, a recent prospective open-label trial of patients 70 years and older found a significant survival advantage with carboplatin and weekly paclitaxel doublet chemotherapy with compared to gemcitabine or vinorelbine monotherapy, suggesting the standard treatment of older patients should be reconsidered.[128]

Tumor histology may also be an important consideration for treatment selection and efficacy. In a phase III study[4,129] that randomized advanced non-small cell lung cancer patients to either cisplatin with pemetrexed or cisplatin with gemcitabine, no significant difference in median survival was found between the two regimens overall. However, when patients with adenocarcinoma were evaluated separately, overall survival was significantly greater among patients receiving cisplatin with pemetrexed compared to those receiving cisplatin with gemcitabine (median survival 12.6 vs. 10.9 months; HR = 0.84; 95% CI, 0.71 to 0.99; $P = .03$); conversely, when patients with squamous cell carcinoma were evaluated, overall survival was significantly greater in the cisplatin with gemcitabine group (median survival 9.4 vs. 10.8 months; HR = 1.23; 95% CI, 1.00 to 1.51; $P = .05$). The differential efficacy of pemetrexed according to histology was also found in a secondary analysis of a phase III trial evaluating second-line treatment with either pemetrexed or docetaxel.[130] The consistency of differential efficacy across studies confirms the survival advantage for pemetrexed in patients with nonsquamous histology, but also points out its activity is limited to 70-80% of NSCLC tumors as pemetrexed is not efficacious in patients with squamous histology.[128]

Second-line treatment with single-agent chemotherapy may be necessary and feasible in advanced NSCLC patients whose disease has progressed during or after first-line, platinum-based

chemotherapy. This treatment option extends to elderly patients who received prior chemotherapy as evidence indicates that efficacy and toxicity is similar between younger and older patients.[131] Monotherapy is preferred in the second-line setting as combination regimens are associated with greater toxicity and no improvement in overall survival compared to single-agent chemotherapy in previously treated patients.[132] Currently, docetaxel and pemetrexed are the only cytotoxic agents approved by the FDA for second-line monotherapy.

Given that advanced non-small cell lung cancer is incurable, a goal of treatment is to maximize the quality of life of the patient by balancing the palliative effects of chemotherapy against toxicity, cost, and the potential burden of frequent treatment administrations. Current evidence supports the use of first- and second-line chemotherapy in patients with advanced non-small cell lung cancer and good performance status, as treatment can significantly prolong survival and successfully manage symptoms. However, the use of cytotoxic chemotherapy beyond second-line treatment is not recommended;[55] administration of third- and fourth-line chemotherapy provides little benefit to overall survival but significantly increases toxic effects.[133] Thus, in patients whose disease progresses beyond second-line chemotherapy, further approved treatment is currently limited to the use of erlotinib, a targeted oral anticancer medication, or best supportive care. The role of targeted therapies and the use of best supportive care are each described in the two sections that follow.

2.1.4.5 Targeted therapy: Bevacizumab

Bevacizumab is a recombinant monoclonal antibody that targets the vascular endothelial growth factor (VEGF) pathway. VEGF is a multifunctional cytokine that stimulates vascular endothelial cells to migrate and divide, form new blood vessels, and protects endothelial cells from apoptosis and senescence; overexpression of VEGF in cancer cells promotes angiogenesis, vascularization, and allows tumors to enlarge and metastasize.[134] Inhibition of tumor vascularization may reduce the supply of oxygen and nutrients to the tumor thereby slowing tumor growth.[135] Thus,

VEGF represents a critical component of tumor development and is an important therapeutic target. Bevacizumab is the only treatment currently approved for use in non-small cell lung cancer that targets VEGF; bevacizumab binds to and neutralizes VEGF, thereby blocking angiogenesis and tumor growth.[136]

Bevacizumab first received FDA approval for the first-line treatment of metastatic colorectal cancer in February of 2004. Approximately two and a half years later, in October of 2006, the FDA approved the use of bevacizumab in combination with carboplatin and paclitaxel for the first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic, non-squamous, non-small cell lung cancer. Treatment with bevacizumab is restricted to patients with non-squamous NSCLC tumors based on evidence from an early phase II study in which squamous cell histology was correlated with an increased risk of serious pulmonary hemorrhage including life-threatening bleeding.[57] FDA approval of bevacizumab for the treatment of advanced NSCLC followed results of the phase III ECOG 4599 trial[56] evaluating the use of bevacizumab in combination with carboplatin and paclitaxel in previously untreated patients with advanced non-small cell lung cancer and a performance status of 0 or 1. The addition of bevacizumab prolonged both progression-free survival (6.2 months vs. 4.5 months) and overall survival (median survival 12.3 months vs. 10.3 months) compared to chemotherapy alone; in a separate analysis[137] of trial results by histology, the prolongation of overall survival was particularly significant among patients with adenocarcinoma (median survival 14.2 months vs. 10.3 months). However, patients receiving bevacizumab were more likely than those receiving chemotherapy only to experience grade 4 neutropenia (25.5% vs. 16.8%) and thrombocytopenia (1.6% vs. 0.2%) as well as grade 3 rash (2.3% vs. 0.5%) and grade 3 or greater bleeding events (4.4% vs. 0.7%).[56] In addition, fifteen treatment-related deaths occurred in the bevacizumab arm compared to just two in the chemotherapy-only arm.

In the recent phase III Avastin in Lung (AVAiL) trial[138] that evaluated the use of bevacizumab in combination with gemcitabine and cisplatin as first-line therapy for non-squamous NSCLC, progression-free survival was significantly improved among patients receiving bevacizumab

compared to those receiving placebo; median overall survival exceeded 13 months but was not significantly different between groups, possibly due to the use of efficacious second-line therapies during the trial. The overall incidence of grade 3 or greater toxicities was similar across treatment groups, but incidence of severe toxicities was higher among patients receiving high-dose (15mg/kg) bevacizumab compared to patients receiving either low-dose (7.5mg/kg) or placebo. Also, severe pulmonary hemorrhage was increased among patients receiving bevacizumab, including seven fatal cases; however, the rate of pulmonary hemorrhage was similar to that seen in the ECOG 4599 trial of bevacizumab with carboplatin and paclitaxel.[139]

Use of bevacizumab in addition to carboplatin and paclitaxel in healthy elderly patients did not result in an increase in overall survival compared to carboplatin and paclitaxel alone (median survival 11.3 months vs. 12.1 months; HR = 0.87; 95% CI, 0.64 to 1.19; $P = 0.4$). However, the combination of bevacizumab with carboplatin and paclitaxel was associated with a significant increase in grade 3 to 5 toxicities compared to carboplatin and paclitaxel alone (87% vs. 61%). In addition, elderly patients had a higher incidence of grade 3 or greater neutropenia and bleeding with the use of bevacizumab compared to younger patients. In a subgroup analysis of the AVAiL trial,[6] patients aged 65 years and older who received bevacizumab had similar reductions in the risk of progression or death versus placebo as patients younger than 65 years. In addition, the overall incidence of adverse effects among elderly patients was similar to that of younger patients. Grade 3 or greater thrombocytopenia occurred more often with bevacizumab in older patients, but the incidence of other severe adverse effects was similar between older and younger patients.[6]

Other clinical trials continue to evaluate the role of bevacizumab in advanced non-small cell lung cancer, including its use with alternative chemotherapy regimens for first-line treatment, and its use with or without other therapies for second-line or maintenance treatment. Current evidence from several phase II trials suggests that bevacizumab is well tolerated and shows promise in improving overall survival with other platinum-based regimens for first-line treatment of advanced non-squamous NSCLC, including carboplatin/docetaxel,[140] carboplatin/gemcitabine,[141]

carboplatin/pemetrexed,[142] oxaliplatin/pemetrexed,[143] oxaliplatin/gemcitabine.[144] Results of future trials will provide additional insight on how bevacizumab fares as maintenance treatment following initial platinum-based doublet therapy, including how bevacizumab compares to currently approved maintenance treatments such as pemetrexed.[145]

2.2 Population Differences in Non-Small Cell Lung Cancer

2.2.1 Age

2.2.1.1 Diagnosis and stage

Lung cancer is a disease that generally affects older adults; nearly 70% of diagnoses occur in patients aged 65 years or older.[2] Although the incidence of lung cancer in the United States has been decreasing over the last decade, particularly in younger age groups, the incidence rate remains significantly higher in older adults and has increased in adults 75 and older.[10] For example, from 2000 to 2008, the incidence rate of cancer in the lung and bronchus among adults between ages 20 and 49 decreased from approximately 8 individuals per 100,000 in 2000 to 6 per 100,000 in 2008. Among adults aged 50 to 64, the incidence rate decreased from 113 per 100,000 in 2000 to 87 per 100,000 in 2008. Furthermore, the rate also decreased among adults aged 65 to 74 years, going from 330 per 100,000 in 2000 to 308 per 100,000. Conversely, the incidence rate in adults aged 75 years and older went from 365 per 100,000 in 2000 to a peak of 407 per 100,000 in 2007 and has now begun to decline with approximately 399 cases per 100,000 in 2008.[10]

Although the incidence rate is much higher among older adults, younger adults with non-small cell lung cancer have a greater proportion of distant stage disease at diagnosis.[10] In the SEER database from 2000 to 2008 and among adult cases age 20 to 49, approximately 13% presented with localized disease, 22% with regional spread, 61% with distant metastases, and 5% were unstaged at diagnosis. In comparison, among adult cases aged 65 to 74, approximately 18% presented with

localized disease, 23% with regional spread, 52% with distant metastases, and 7% were unstaged. Adult patients age 75 and older had similar rates of localized and metastatic disease as patients age 65 to 74, but only 19% presented with regional spread and 13% were unstaged at diagnosis.[10] Similar findings were present in a single-institution study of patients undergoing surgical resection at a hospital in California.[146] Among patients under the age of 50, greater than 54% presented with metastatic disease compared to 45% or less of patients in the age groups 60 to 69, 70 to 79, or 80 and older. Also, localized disease was present in just 20% of patients under the age of 50 compared to 30% or more in the older age groups.[146]

2.2.1.2 Treatment

It has been established that older adults are underrepresented in cancer clinical trials,[11,12] which limits our knowledge about the potential benefits and harms associated with various treatments in patients aged 70 years and older. Much of our understanding about the efficacy and safety of treatment in older adults is established through post hoc analyses of clinical trials comparing outcomes between older and younger patients. However, the limited number of adults over the age of 70 enrolled in clinical trials and the tendency for clinical trial participants to be in better overall health compared to the general population restricts the generalization of clinical trial data. As a result, clinicians may be hesitant to recommend or use certain treatments for older patients, particularly those treatments that may be difficult for older adults or patients with less than optimal performance status to tolerate, such as surgery and chemotherapy. Unfortunately, chronological age may act as a proxy for poor performance status in the clinical setting despite the heterogeneity of performance status among older adults age 65 to 70 years and older. Older patients in good health may be denied access to more effective or novel treatments because of their age rather than clinical factors that are more representative of the patient's ability to tolerate and receive benefit from treatment.

Given that patients participating in clinical trials are randomized to treatment or placebo, understanding of the use of specific treatments and the clinical and non-clinical factors associated with their use is dependent on retrospective evaluations of observational data. Several analyses using such an approach with SEER-Medicare data provide insight into the use and outcomes of various treatments among older adults with non-small cell lung cancer. One such study evaluated the use of surgical resection among older adults diagnosed with stage I or II non-small cell lung cancer between 1985 and 1993.[2521] Although their main independent factor of interest was race, differences in the use of surgical resection across chronological age groups were apparent. In both black and white patients, the use of surgical resection declined with increasing age including a decrease of 15% or more between patients age 70 to 74 and patients age 75 and older. Another study evaluating the use of surgical resection among older adults diagnosed with stage I NSCLC between 1995 and 2004 also found a decline in surgical resection with increasing age; 90% or more of patients in age groups ≤ 60, 61 to 70, and 71 to 80 received surgical resection compared to less than 80% of patients 80 years and older.[147] Furthermore, an analysis of treatment use among older adults diagnosed with stage I through IV NSCLC between 1988 and 2003 found that the use of surgery and/or radiation declined with increasing age and that nearly half of patients 80 years and older received no initial treatment after diagnosis compared to approximately 30% of patients age 70 to 79, and 20% of patients younger than 70 years of age.[148] These age differences in surgical resection and radiation therapy remain even after controlling for other factors that influence the receipt of treatment, such as marital status, comorbidity, and socioeconomic status.[18,20]

Disparity across age groups regarding the use of chemotherapy for advanced stage NSCLC is of particular concern given the risk-benefit tradeoff of cytotoxic therapy. Clinical trials have shown that chemotherapy, particularly platinum-based doublet chemotherapy, improves quality of life and overall survival in patients with advanced NSCLC.[55] However, chemotherapy also carries the risk of treatment toxicity, including a potential risk of life-threatening adverse effects that may prevent clinicians from administering chemotherapy to older patients, particularly if the expected benefit of

treatment is small. Previous analyses of SEER-Medicare data clearly indicate that chronological age is in fact an independent predictor of chemotherapy use among patients with advanced non-small cell lung cancer. For example, among patients diagnosed with stage III of IV NSCLC between 1994 and 1999, patients age 75 years and older were significantly less likely to receive chemotherapy compared to patients under the age of 75 (OR 0.91; 95% CI 0.91, 0.92).[149] Similar results were observed among cases of stage III or IV NSCLC diagnosed between 1991 and 2002 where patients in age groups 70-74 years (OR 0.81; 95% CI 0.77, 0.85), 75-79 years (OR 0.54; 95% CI 0.51, 0.57), 80-84 years (OR 0.30; 95% CI 0.28, 0.32), and 85 years or older (OR 0.16; 95% CI 0.14, 0.18) were all significantly less likely to receive chemotherapy treatment compared to patients age 65-69.[18] In addition, a comparable analysis of stage III or IV cases diagnosed through 2002 in the SEER-Medicare data found that patients in age groups 70-74 years (OR 1.32; 95% CI 1.09, 1.59), 75-79 years (OR 1.86; 95% CI 1.53, 2.26), 80-84 years (OR 4.03; 95% CI 3.20, 5.08), and 85 years or older (OR 7.24; 95% CI 5.06, 10.35) were all significantly more likely to receive single agent as opposed to platinum-based doublet chemotherapy compared to patients age 66-69.[15]

Data sources other than SEER-Medicare have also been used in retrospective analyses of chemotherapy use among older adults with advanced NSCLC. For example, Rasco et al.[150] evaluated individuals diagnosed with stage IV NSCLC from 2000 to 2007 at the University of Texas Southwestern Medical Center and found in their multivariable analysis that patients under 65 years of age were more likely than patients age 65 years and older to receive chemotherapy (OR 1.96; 95% CI 1.26, 3.06). However, a potentially important limitation of the study was that although the authors considered sociodemographic factors such as race and insurance status in their analysis, they did not control for important clinical characteristics including patient performance status or comorbidities that may further predict the use or non-use of chemotherapy in older adults with advanced NSCLC. Conversely, the presence of cardiovascular disease, pulmonary disease and a measure of the severity of comorbidity was accounted for in a study of participants from the Cancer Care Outcomes Research and Surveillance Consortium with newly diagnosed stage IIB or IV NSCLC between 2003 and

2005.[151] In the unadjusted analysis of chemotherapy use, 78.7%, 64.0%, 60.5%, and 42.4% of patients under the age of 55, age 55-64 years, age 65-74 years, age 75 years and older, respectively, received chemotherapy treatment. In addition, approximately 85% of patients under the age of 65 received platinum-based chemotherapy compared to less than 78% of patients age 65-74 years and less than 68% of patients age 75 years and older. After adjusting for clinical and sociodemographic factors, including those previously mentioned, age remained an important predictor of chemotherapy use and use of a platinum-based regimen among those patients receiving chemotherapy.

The results of several observational studies clearly indicate that chronological age is an important predictor of treatment, including surgical resection and chemotherapy use, two treatments that carry a greater risk for complications and/or toxicity. Perhaps it is the belief that the oldest of older adult patients have limited life expectancy and would receive little benefit from surgical resection or chemotherapy that influences the disparate use of these therapeutic modalities among older adults with NSCLC. However, chronological age alone is not the most appropriate determinant of care. The overall health and performance status of patients within an age group can vary significantly and, in turn, influence the use and outcomes of available treatments. As will be described in the section that follows, older patients with good overall health may benefit from surgical resection of localized disease as well as from chemotherapy for advanced NSCLC. At the same time, older patients who are frail may have extreme difficulty tolerating such treatments, may experience life-threatening toxicity and stand to gain little overall benefit from them. Still, despite evidence to support the use of certain treatments in select older lung cancer patients, chronological age remains a factor in determining whether patients receive guideline-recommended treatment; as a result, a significant proportion of older patients fail to receive more aggressive therapy from which they may benefit.[15]

2.2.1.3 Survival

Although mortality has improved slightly over the last few decades, survival remains poorest among patients ages 75 and older.[10] The relative 1-year survival of lung and bronchus cases diagnosed between 1988 and 2007 in SEER registries is 49.9%, 47.1%, 42.6%, and 33.7% among patients ages 20-49 years, 50-64 years, 65-74 years, and 75 years or older is 20.9% 17.6%, 15.2% and respectively. Also, the 5-year survival of the same cases is 20.9%, 17.6%, 15.2%m and 10.4%, among patients ages 20-49 years, 50-64 years, 65-74 years, and 75 years or older, respectively. Differences in the duration of survival among age groups are partly due to a relatively limited life expectancy among older adults as they are closer to the end of the natural lifespan and may be at greater risk of death from other causes. However, survival differences may also be explained by decreased utilization of lung cancer treatments that may cure disease and/or prolong overall survival. Furthermore, even among patients diagnosed over the age of 80, the argument that a limited life expectancy among older adults negates the usefulness of treatment is challenged from national life table data that shows that 75-year-old to 85-year-old Americans have a conditional life expectancy of 11.6 to 6.8 years.[152] Therefore, it seems reasonable that older healthy patients should be offered potentially curable surgical resection as well as chemotherapy and targeted treatments that may not only prolong survival, but also improve the quality of life. However, given the low representation of older adults in clinical trials and the hesitancy to ascribe certain treatments such as surgical resection and chemotherapy to the oldest of older patients, knowledge of the efficacy and safety of these treatments in older adults is largely reliant on post-hoc analyses of clinical trials and retrospective analyses of observational data.

The benefit of surgical resection among older adults with early stage disease has been evaluated in several observational analyses, with some differences in the results. Interestingly, in a study of SEER-Medicare cases of stage I or II NSCLC diagnosed between 1985 and 1993, older age (70 or older) was significantly associated with poorer survival even when controlling for race,

income, comorbidity, and receipt of surgical resection.[25] However, in a similar study of patients with stage I NSCLC diagnosed between 1995 and 2004, despite a lower rate of surgical resection among older adults, there were no significant differences in survival with respect to age among resected patients; lung cancer was found to be the major contributor to mortality among patients who did not receive surgery, even among the oldest patients, which suggests that surgical resection should be considered in elderly patients when feasible.[147] In a retrospective analysis of patients with NSCLC treated at a single-institution, older adults were less likely to receive surgical resection for localized or regional-stage disease, but 5-year survival rates among patients age under 50, age 50-59 years, age 60-69 years, age 70-79 years, and age 80 years or older were comparable across groups.[146]

There has been continued debate over the use of chemotherapy among older adult patients with NSCLC, particularly the use of platinum-based doublet chemotherapy for patients with advanced stage disease. Information regarding the efficacy of chemotherapeutic agents among older adults with NSCLC has been largely gained from post-hoc or subgroup analyses of phase II and phase III clinical trials. For instance, the use of chemotherapy in elderly patients with early-stage disease was evaluated in a phase III trial subgroup analysis[153] of vinorelbine with cisplatin following complete surgical resection of stage IB or II NSCLC. Patients over the age of 65 received significantly fewer doses as well as significantly lower average dose-intensities of cisplatin and vinorelbine compared to patients 65 years old and younger. However, overall survival between the two groups was not statistically significant (HR for ≤ 65 vs. > 65, 0.77; 95% CI 0.57, 1.03); patients over the age of 65 received a benefit in survival (HR, 0.61; 95% CI 0.38, 0.98) that was similar to the effect seen in the total trial population. Still, when age was categorized into smaller groups, the survival benefit seemed to disappear among patients over the age of 75 (HR, 2.35; 95% CI 0.84, 6.58), although there were only 12 patients in the chemotherapy arm and 11 in the observation arm for this group.

Most analyses of clinical trial data regarding the use of chemotherapy in older adults with NSCLC have focused on the use of chemotherapy in advanced stages of disease. In a clinical trial designed specifically for the evaluation of single-agent vinorelbine treatment in patients 70 years or

older with stage IIIB or IV NSCLC and performance status of 0, 1, or 2, patients who received vinorelbine had significantly greater survival at 1-year compared to patients in the control arm (32% vs. 14%), and after adjusting for stage of disease and performance status, vinorelbine was associated with a significant survival advantage (HR, 0.65; 95% CI 0.45, 0.93).[154] A follow-up study comparing single-agent treatment with either vinorelbine or gemcitabine with the doublet therapy of vinorelbine and gemcitabine among patients 70 years or older found no survival benefit with the combination treatment and increased toxicity compared to either of the single-agent regimens.[155]

Several subgroup analyses of clinical trials have examined the benefit of platinum-based chemotherapy in older adults. For instance, Langer et al.[156] carried out a subgroup analysis of older patients with stage IIIB or IV NSCLC and performance status of 0 or 1 who were randomized to receive cisplatin plus either etoposide or paclitaxel as first-line treatment. Overall survival was similar between patients age 70 years and older and patients under the age of 70 (median survival 8.5 months vs. 9.0 months) as was 1-year survival (29% vs. 38%). Belani et al.[127] performed a subgroup analysis of adults 65 years and older who participated in a phase III trial comparing docetaxel/cisplatin (DC), docetaxel/carboplatin (DCb), and vinorelbine/cisplatin (VC) for first-line treatment of chemotherapy-naïve patients with stage IIIB or IV NSCLC. Patients age 65 and older and patients under the age of 65 had similar estimates for median survival, 1-year survival, and 2-year survival in each of the three treatment arms. Furthermore, both older and younger patients randomized to DC had higher median survival, 1-year and 2-year survival than patients randomized to VC.[127] A phase III trial evaluation of carboplatin and paclitaxel for the treatment of stage IIIB or IV NSCLC also demonstrated that patients age 70 years and older received similar benefit as patients under the age of 70 with regard to both overall survival (median survival 7.1 months vs. 7.8 months) and 1-year survival (33% vs. 30%).[157] Conversely, a pooled analysis of patients from two separate Southwest Oncology Group trials found that although patients age 70 and older derived benefit from either cisplatin and gemcitabine or carboplatin and paclitaxel, overall survival and 1-year survival rates were better

among patients under the age of 70 (median survival, 7 months vs. 9 months; 1-year survival, 27% vs. 40%).[158]

SEER-Medicare analyses have also evaluated the effectiveness of chemotherapy among older adults with advanced stage NSCLC. For example in a study of patients aged 65 and older with stage IV NSCLC diagnosed between 1991 and 1996, chemotherapy use was associated with prolonged survival (HR, 0.81; 95% CI 0.76, 0.85); furthermore, analysis with instrumental variable methods indicated an increase in survival of 33 days and an increase in 1-year survival of 9% with chemotherapy use.[159] A study by Ramsey et al.[149] also evaluated the use and outcomes of chemotherapy among patients diagnosed with stage IIIB or IV NSCLC between 1994 and 1999, and found that although adult patients 75 years and older were significantly less likely to receive treatment there was no relationship between age and survival in their multivariate analysis. However, an analysis of patients with stage III or IV NSCLC diagnosed between 1997 and 2002 revealed that despite a survival benefit from the receipt of chemotherapy, increasing age remained associated with increasing mortality risk; the hazard ratio was 4% to 12% higher (statistically significant) among patients ages 70 to 85 and older compared to patients ages 66 to 69. Still, there were no significant age group differences with regard to the survival benefit of platinum-based doublet chemotherapy over single-agent treatment.[15]

Although the use of targeted therapy is a relatively new treatment modality in non-small cell lung cancer, the potential benefit of extending overall survival in healthy older adults beyond the rather stagnant 10 to 11 months with doublet chemotherapy has prompted publication of two subgroup analyses of phase III clinical trials involving the use of bevacizumab.[18,58] In a subgroup analysis of patients aged 65 years or older in the AVAiL trial, patients received cisplatin and gemcitabine for up to 6 cycles in addition to either low dose (7.5 mg/kg) or high dose (15 mg/kg) bevacizumab or placebo.[6] Overall survival in each arm of bevacizumab was favorable versus placebo (HR for 7.5 mg/kg, 0.84; HR for 15 mg/kg, 0.88) although neither treatment arm resulted in a statistically significant benefit. Conversely, in a subgroup analysis of the ECOG 4599 trial that lead to

the approval of bevacizumab for treatment of advanced NSCLC, patients aged 70 years and older who were randomized to receive bevacizumab (15 mg/kg) in addition to carboplatin and paclitaxel received no benefit in overall survival compared to patients of the same age group who received carboplatin and paclitaxel only (median survival, 11.3 months vs. 12.1 months). Furthermore, a recent analysis[7] of older adults with advanced NSCLC (stage IIIB and stage IV) in the SEER-Medicare database found no significant survival advantage among older patients receiving bevacizumab with carboplatin-paclitaxel chemotherapy compared to older patients receiving carboplatin-paclitaxel chemotherapy alone (multivariable-adjusted HR 1.01, 95% CI 0.88-1.15). Given the lack of overall survival benefit in subgroup analysis of clinical trials or observational studies, it remains unclear whether bevacizumab should be considered in addition to standard platinum-based doublet chemotherapy among older adults aged 65-70 years or older.

Other than the study by Zhu et al.[7] of older adults receiving carboplatin-paclitaxel chemotherapy with or without bevacizumab, no observational analyses have been published regarding the use and outcomes of bevacizumab in advanced non-small cell lung cancer. By including patients treated with a broader range of platinum-based doublet chemotherapy regimens (i.e., supplementary to carboplatin-paclitaxel), the addition of retrospective analyses with larger treatment group sizes could provide greater insight about the potential benefit of bevacizumab among older patients with advanced NSCLC, particularly whether or not younger subgroups of fit older adults (e.g., 65 to 69 years) benefit compared to older subgroups (e.g., 75 to 79 years).

2.2.1.4 Adverse effects

A large concern with the use of systemic chemotherapy and targeted therapies such as bevacizumab among older patients with advanced NSCLC is the potential for severe toxicity, especially toxicity that can be life-threatening, decrease quality of life, and diminish or outweigh any potential benefit in overall survival. As with the efficacy of chemotherapy and bevacizumab, subgroup analyses of clinical trials and retrospective analyses of observational data provide the

evidence currently available regarding the tolerability of these agents among older patients with advanced non-small cell lung cancer. In an evaluation of cisplatin-based treatment among elderly patients with advanced NSCLC participating in the ECOG 5592 trial, toxic effects were generally similar between younger (< 70 years) and older (70 years and older) patients despite significantly greater cardiovascular and pulmonary comorbidity among older patients at baseline.[156]

Patients 65 years and older tolerated and benefited from platinum-docetaxel combination therapy in a subgroup analysis a phase III trial comparing docetaxel/cisplatin (DC), docetaxel/carboplatin (DCb), and vinorelbine/cisplatin (VC).[127] When compared to patients less than 65 years of age, older patients had slightly increased grade 3-4 non-hematologic and hematologic toxicities, including a greater incidence of leukopenia and neutropenia in the platinum-docetaxel arms. Despite a trend toward significance for greater neutropenia among older (70 years and older) patients with stage IIIB or IV NSCLC who received cisplatin/gemcitabine or carboplatin/ paclitaxel in a pooled analysis of two separate Southwest Oncology Group trials, grade 3-5 hematologic and non-hematologic toxicities were similar between older and younger patients.[158] Furthermore, additional evidence that fit older patients can tolerate platinum-based chemotherapy is provided in a subgroup analysis of patients randomized to receive carboplatin/paclitaxel which found that younger (< 70 years) and older (70 years and older) patients had similar rates of grade 3-4 hematologic and non-hematologic toxicities.[157] Combined with the improvement in overall survival, evidence of tolerability with the of carboplatin and paclitaxel shows that fit older patients with advanced non-small cell lung cancer stand to benefit from platinum-based doublet chemotherapy and that chronological age alone is a poor determinant of whether or not older patients should receive treatment with these agents.

In a study of the SEER-Medicare data that included patients diagnosed with stage I to IV NSCLC between 1991 and 2002, chemotherapy use was not associated with the development of cardiac conditions in a crude analysis model.[160] However, in a multivariable analysis that accounted for age, stage at diagnosis, and comorbidity, chemotherapy use was associated with an increased risk of ischemic heart disease, cardiac dysfunction and heart failure; increased age, particularly age 80

years and older, was also associated with increased risk for cardiac functions in the multivariable model. With the lack of an association between chemotherapy and cardiac conditions in unadjusted analyses and the relationship between each of the conditions and increased age, it is difficult to determine what the true association between chemotherapy use and toxicity is among older adults in the study.

In a cohort of adults from the Cancer Care Outcomes Research and Surveillance Consortium diagnosed with stage IIIB or IV NSCLC between 2003 and 2005, patients aged 65-74 and patients aged 75 or older had a higher rate of any adverse events during chemotherapy compared to patients younger than 55 years of age (IRR for patients 65-74, 1.70; 95% CI 1.19, 2.43; IRR for patients 75 and older, 1.34; 95% CI 0.90, 2.00).[151] Further, compared to patients younger than 55 years of age, older patients had higher rates for specific adverse events, including higher incidences of neuropathy, fever with neutropenia, and sepsis. However, higher incidence rates were only statistically significant between patients aged 65-74 and patients younger than 55 for the incidence of either neuropathy, fever with neutropenia, and sepsis (IRR, 2.03; 95% CI 1.01, 4.08). Thus, although the adjusted incidence rate estimates for toxic effects with chemotherapy use are greater among older adults, the variation around the estimates creates a bit of uncertainty as to whether or not the risk of adverse events is really increased among the oldest patients.

The safety of bevacizumab among older adults has been limited to two subgroup analyses of clinical trials, one conducted in Europe[6] and the other in the United States.[5] In the former study, patients received cisplatin and gemcitabine plus either low dose (7.5 mg/kg) or high dose (15 mg/kg) bevacizumab or placebo. Toxicity patterns between patients aged 65 years and older and patients younger than 65 years were generally similar in this study including similar percentages of patients in the bevacizumab arms who reported at least one grade 3 or higher adverse effect. Notably, approximately 40% of older patients receiving either low or high dose bevacizumab had grade 3 or greater thrombocytopenia compared to less than 30% of younger patients. In the US-based study, adults aged 70 years and older who received bevacizumab (15 mg/kg) in addition to

carboplatin/paclitaxel were more likely to have grade 4 or 5 neutropenia (34% vs. 22%), febrile neutropenia (6.2% vs. 0.9%), and thromobocytopenia (3.5% vs. 0%) compared to older patients who received carboplatin/paclitaxel only. In addition, among patients receiving bevacizumab, older patients were significantly more likely than younger patients to have grade 4 neutropenia as well as grade 3-5 GI bleed, proteinuria, muscle weakness, neuropathy, and dizziness. By comparison, among patients receiving carboplatin/paclitaxel only, no significant differences were found between older and younger patients for the same adverse effects just listed. The lack of benefit from bevacizumab and the greater risk for severe toxicity among older adults in clinical trials brings into question the utility of bevacizumab in the older population of patients with advanced non-small cell lung cancer.

2.2.2 Race

2.2.2.1 Diagnosis and stage

Racial and ethnic disparities exist in the incidence and stage at diagnosis of non-small cell lung cancer in the U.S.[2,26] The burden of disease is disproportionately greater for black males who are more likely to be diagnosed with and die from lung cancer. Black men have the highest incidence rates of lung cancer among all racial, ethnic and gender groups; despite a steady decline since the mid-1980s, the incidence rate of lung cancer among black men in 2007 was 95.4 per 100,000 compared to a rate of 72.1 per 100,000 among white men.[2] However, racial differences in the incidence rates among women have historically been much smaller. In 2007 the incidence rate of lung cancer among black women was 58.1 per 100,000 compared to a rate of 55.1 per 100,000 among white women.[2]

Blacks are also more likely to be diagnosed at advanced stages of disease.[2,26] Among all cases diagnosed in the United States between 1999 and 2006, 15% were diagnosed at a localized stage, 22% had spread to regional lymph nodes, and 56% had distant metastases at the time of diagnosis. When these cases were stratified by race, 15% of whites were diagnosed with localized disease, 22%

with regional spread, and 55% with distant metastases. However, only 12% of blacks were diagnosed at a localized stage and 60% were diagnosed with distant metastases. The reasons behind these racial disparities in cancer incidence, although not entirely clear, are likely to include a combination of biological, environmental, and cultural influences including genetics, access to health care and smoking prevalence.

2.2.2.2 Treatment

Race and ethnicity may be important factors that influence the use and outcomes of staging procedures and treatment for non-small cell lung cancer. Staging methods, both invasive and non-invasive, allow physicians to determine the prognosis and appropriate treatment options available to patients. However, evidence suggests that the use of staging procedures may not be consistent across racial groups and contribute to differences in the use of related treatments. In a study of the Surveillance, Epidemiology, and End Results (SEER) data from 1991 to 2001, blacks with non-metastatic NSCLC were 25% less likely than whites to undergo invasive staging with bronchoscopy, mediastinoscopy, or thoracoscopy;[161] even when blacks underwent invasive staging, they were significantly less likely to receive a recommendation for or undergo surgery. A more recent evaluation of patients diagnosed between 1994 and 2004 in the California Cancer Registry did not find an association between race and the use of either invasive or non-invasive staging, but black patients were less likely to undergo surgery compared to whites regardless of staging use.[162] While the relationship between race and the use of staging procedures is less clear, the association between race and a decreased utilization of curative surgery for lung cancer has been a consistent finding in studies. For example, in an early study by Greenwald et al., whites were 20% more likely to undergo curative surgery for early-stage disease.[61] In a study by Bach et al.[25] examining the use of surgery among patients diagnosed between 1985 and 1993 in SEER-Medicare, 76.7% of whites received surgery compared to only 64.0% of black patients, a difference that remained significant after

adjusting for factors that predicted surgical candidacy. Similar findings were realized in a study of patients diagnosed between 1996 and 2002 in the South Carolina Cancer Registry which found that blacks were significantly less likely than whites to undergo surgical resection (44.7% vs. 63.4%).[163] Furthermore, the difference in receipt of surgery for early stage lung cancer is not limited to the comparison between blacks and whites. Evaluation of patients diagnosed between 1991 and 2000 in the SEER registry demonstrated that Hispanics were also less likely than non-Hispanic whites to receive surgical resection of early stage NSCLC and that the disparity in surgical resection explains any differences seen in survival.[17] Similarly, compared to whites, American Indian and Alaskan Natives are more likely to be diagnosed with advanced stage disease and less likely to undergo surgical resection, but have similar survival outcomes to whites and other racial/ethnic groups when stage and treatment are equal.[19]

Several factors may influence the disparity in surgical resection seen among racial and ethnic groups. In a study of the California Cancer Registry data between 1989 and 2003, low socioeconomic status was more common among black and Hispanic patients with stage I NSCLC and was significantly associated with fewer surgical resections performed and worse survival.[164] In a prospective cohort study of patients with early-stage operable lung cancer in which only 62 of 113 (55%) black patients chose surgery compared to 179 of 273 (66%) of white patients, the presence of two or more comorbid conditions and the lack of a regular source of care were significant predictors of a decision against surgery in black patients but not in whites.[27] The relationship between greater comorbidity, black race and non-receipt of surgical treatment was also found in a retrospective analysis of medical records for nearly 1,200 patients identified through the Josephine Ford Cancer Center Tumor Registry.[38] In a separate retrospective cohort study of patients seen at the pulmonary clinic of the Henry Ford Health System in Detroit, MI, race was not a significant predictor of being offered surgical treatment after controlling for influential clinical characteristics, but the surgical rate was significantly lower among black patients than in whites (58% vs. 74%) suggesting that black patients were less likely to accept surgical treatment.[33] A retrospective analysis of patients diagnosed

between 1992 and 2002 in the SEER-Medicare basis also found that blacks were less likely to undergo recommended surgical therapy than whites (69% vs. 83%); the authors of the study suggest that distrust of the healthcare system, differences in the beliefs and perceptions about lung cancer and its treatment, and limited access to care are likely to explain racial disparities in surgical resection of non-small cell lung cancer.[23] In addition, lower acceptance of surgical treatment among black patients may be related to less engaging relationships and poorer, less effective communication with providers.[27]

Besides lower rates of surgical resection compared to whites, blacks are also less likely to receive chemotherapy for advanced stages of lung cancer and are less likely to receive appropriate treatment in a timely manner.[18,20,24,41,58,165] For example, an early study of metastatic NSCLC cases diagnosed between 1991 and 1993 in SEER-Medicare revealed that black patients were 30% less likely to receive chemotherapy compared to whites (OR 0.70; 95% CI 0.55-0.88).[41] Furthermore, in an analysis of NSCLC cases in the SEER-Medicare database between 1995 and 1999, Shugarman et al.[20] found black patients were significantly less likely than whites to receive timely and clinically appropriate treatment for each stage of NSCLC; black patients were 66% less likely to receive timely surgical resection for stage I or II disease, 34% less likely to receive timely chemotherapy, radiation, and/or surgical resection for stage III disease, and 51% less likely to receive chemotherapy for stage IV disease. Perhaps important to note, based on the findings of additional studies using SEER-Medicare data that have indicated that the use of radiation therapy does not vary by race or ethnicity,[18,166] the lower receipt of treatment among blacks compared to whites with stage III NSCLC is most likely due to lower utilization of chemotherapy and/or surgery than to less use of radiation.

An analysis of SEER-Medicare cases between 1991 and 2002 by Hardy et al.[18] resulted in similar findings to the Shugarman et al. study. Blacks were 37% less likely to receive surgical resection and 42% less likely to receive chemotherapy for stage I or II NSCLC, and 57% less likely to receive chemotherapy for stage III or IV disease compared to whites. Interestingly, when adjusted results from the Hardy study were stratified by years of diagnosis, the odds ratio comparing the

receipt of chemotherapy for stage III or IV NSCLC between black and white patients changed significantly between cases diagnosed in 1991-1995 (OR 0.74; 95% CI 0.35-1.54) or 1996-1999 (OR 0.76; 95% CI 0.39-1.47) and cases diagnosed in 2000-2002 (OR 0.24; 95% CI 0.14-0.40). Based on the findings of disparate use of chemotherapy among racial/ethnic groups in the aforementioned study of metastatic cancer by Earle et al.,[41] the non-significant findings in earlier years of the Hardy et al. study may be more heavily influenced by insignificant differences in chemotherapy use for stage III NSCLC as opposed to stage IV.

Additional analyses of SEER-Medicare, including more recently published studies, have consistently found variation in the use of chemotherapy for advanced NSCLC. A study of patients diagnosed with stage IIIB or IV NSCLC in SEER-Medicare data between 1994 and 1999 found that blacks were about 50% less likely to receive chemotherapy treatment compared to whites; significant differences were not seen between whites and other non-black non-white patients.[149] In a similar study that included stage IIIB or IV NSCLC cases diagnosed between 1997 and 2002 in SEER-Medicare data, black patients were still more than 40% less likely than whites to receive first-line chemotherapy (OR 0.59; 95% CI 0.52, 0.67).[167] Again, although a trend towards a similar disparity was seen when comparing patients of other racial/ethnic groups to whites, the differences were not significant. However, black (OR 0.61; 95% CI 0.48, 0.77), Hispanic (OR 0.46; 95% CI 0.31, 0.67), and Asian (OR 0.49; 95% CI 0.31, 0.76) patients were all significantly less likely than whites to receive doublet chemotherapy with a platinum agent and a taxane, and black patients were also significantly less likely to receive treatment with a platinum agent and gemcitabine compared to whites (OR 0.59; 95% CI 0.35, 0.98). Davidoff et al.[15] completed a separate analysis of advanced NSCLC cases diagnosed between 1997 and 2002 in SEER-Medicare with similar results. Black patients were 38% less likely than white patients to receive any chemotherapy within 90 days of diagnosis (OR 0.72; 95% CI 0.63, 0.82), and were 53% more likely than white patients to receive treatment with single agent chemotherapy as opposed to platinum-based doublet therapy (OR 1.53; 95% CI 1.16, 2.01).

The unequal receipt of chemotherapy treatment among black patients with advanced non-small cell lung cancer may be ascribed to differences in the rate of referral to oncologists, the availability of novel diagnostic technologies, poorer overall health, or the acceptance of treatment options by patients.[27,31-33] In a study of patients over age 65 with metastatic NSCLC diagnosed between 1991 and 1996 in SEER-Medicare, black patients were nearly 50% less likely to receive chemotherapy or see an oncologist compared to white patients.[31] Even among patients who saw an oncologist, blacks remained 36% less likely than white patients to receive chemotherapy.

2.2.2.3 Survival

Mortality from lung cancer remains highest among black patients, although the difference in lung cancer mortality between black and white patients has improved over the last two decades. The greatest difference in mortality rates has been observed between black men and white men; in 2007, the estimated mortality rate among black men was 82.7 per 100,000 compared to a rate of 64.9 per 100,000 among white men. Conversely, black women actually had a slightly lower mortality rate (39.2 per 100,000) compared to the rate among white women (41.1 per 100,000) during the same time period.[2] Two important contributors to the increased mortality seen among black men include the higher incidence rate of lung cancer and greater proportion of black males presenting with incurable stages of disease.[1]

Other underlying causes of the racial disparities seen in mortality rates of lung cancer may be similar to those factors that contribute to disparities in the incidence and treatment of disease, particularly unequal access to and quality of care. Lower income and lack of insurance are significant contributors to disparities in health care access and quality,[30] and because a significant proportion of blacks are poor and/or uninsured,[21] they are less likely to have access to quality health care. Inequitable access to quality care may then lead to disproportionate rates of advanced disease at diagnosis, underutilization of available treatments, and worse survival outcomes.

Despite the fact that treatment of lung cancer across racial and ethnic groups is hardly equal,[17-19,25,27,161] research has shown that when black patients receive treatment equal to that of non-black patients with similar prognoses, equal outcomes are observed.[17,19,24,25,29,58-64] A prime example is the study by Bach et al.[25] that evaluated the use and outcomes of surgical resection among patients diagnosed with stage I or II NSCLC in SEER-Medicare between 1985 and 1993. The rate of surgical resection was approximately 13% lower among black patients compared to whites, and 5-year survival was significantly lower for black patients. However, both unadjusted and adjusted analyses showed that black patients who underwent surgical resection had similar survival benefit to that of white patients who received surgery. Greenwald et al.[61] also examined the use of surgical resection and outcomes among patients diagnosed with stage I NSCLC and found that differences in overall survival between black and white patients disappears when treatment and socioeconomic status are accounted for in the regression model. Furthermore, Wisnivesky et al.[17] found similar results in their comparison of surgical resection and outcomes between Hispanic and white patients; although Hispanic patients were less likely to undergo surgical resection and were more likely to have a lower household income and poorer survival than white patients, the survival difference ceased when surgery and stage were adjusted for. In addition, similar to the Greenwald study, income remained a significant independent predictor of survival.

Equal outcomes with equal treatment is further evidenced in a retrospective analysis of four randomized studies on irradiation treatment for NSCLC conducted by the Radiation Therapy Oncology Group found that, despite variation in the presentation of black and white patients, there was no significant difference in overall survival between the two groups.[60] In a case-control analysis of patients with stage I, II, or III NSCLC, black patients were more likely to be smokers, have lower annual income, a greater delay in receiving treatment, were less likely to accept neo-adjuvant chemotherapy prior to surgical resection, and had worse 5-year overall survival compared to white patients.[24] However, when the poor prognostic factors (i.e., smoking status, socioeconomic status, and refusal of treatment) were controlled for overall survival rates for black and white patients were

similar. In a study of the Florida cancer registry with patients diagnosed between 1998 and 2002, black patients were less likely to receive surgical resection, more likely to receive radiation therapy and have poorer overall survival compared to white patients.[62] However, in multivariable analyses that adjusted for treatment and socioeconomic variables, no difference in overall survival existed between black and white patients; patients in the lowest poverty level and those with no insurance or Medicaid had significantly poorer survival.

Similar survival outcomes between racial and ethnic groups have also been observed with equal use of chemotherapy for advanced stages of NSCLC. In a comparison of white and black patients with stage IIIB or IV non-small cell lung cancer who participated in a three-arm phase III trial of chemotherapy, median survival was greater among black patients overall (9.1 months vs. 8.3 months).[59] An analysis of trials conducted by the Southwest Oncology Group also found no racial disparities in survival among white and black patients with advanced-stage non-small cell lung cancer.[64] However, in an analysis of patients receiving chemotherapy in phase II and phase III Cancer and Leukemia Group B trials found significantly poorer 1-year survival among black patients compared to non-black patients.[63] Yet, when performance status and weight loss were adjusted for in a multivariable analysis, the effect of race on survival disappeared; the authors attributed the greater likelihood of black patients to present in poorer health, with greater weight loss, and less favorable socioeconomic status to poor social circumstances.[63]

Comparable outcomes across racial and ethnic groups have also been observed in analyses using SEER-Medicare data. In patients diagnosed with stage III or IV NSCLC between 1994 and 1999, black patients were significantly less likely to receive chemotherapy compared to white patients, but when treatment was adjusted for in a multivariable hazards model, there was no significant difference in survival between the two groups.[149] An analysis of patients with stage I to IIIA NSCLC diagnosed in SEER between 1998 and 2006 evaluated disparities among American Indians and Alaskan Natives (AI/AN). Similar to black patients, AI/AN patients were more likely than whites to be diagnosed with advanced stage disease, less likely to receive surgical resection, and

have poor overall survival.[19] When treatment was accounted for in a multivariable regression, survival among AI/AN patients remained worse than among whites but the difference was not significant statistically. Finally, in a study of patients with stage I to IV NSCLC in SEER-Medicare diagnosed between 1991 and 2002 in which black patients were significantly less likely than white patients to receive chemotherapy for stage III or IV disease, blacks had worse overall survival in the crude analysis.[58] However, just as with the previous findings in both clinical trials and observational studies, the difference in overall survival between black and white patients disappeared when treatment and socioeconomic status were adjusted for in the proportional hazards model. Receipt of treatment was associated with a 30% reduction in mortality while the lowest socioeconomic status quartile had a 9% increase in mortality compared to the highest quartile. Given the findings of these studies, the evidence supports the idea that lower survival from non-small cell lung cancer among black patients can be largely explained by poorer socioeconomic status, greater likelihood of advanced stage disease and poorer performance status at diagnosis, and lower offering, acceptance or use of appropriate and/or novel treatments.

2.2.2.4 Adverse effects

Few studies have examined the association between race and adverse effects from treatment for non-small cell lung cancer, particularly chemotherapy for advanced stage disease. However there are a couple of analyses that may provide some insight as to whether racial differences exist in relation to the incidence of toxicity following receipt of various treatments. For example, in a multivariable analysis of patients diagnosed with stage I to IV NSCLC in SEER-Medicare between 1991 and 2002, black patients were more likely than white patients to develop cardiomyopathy, cardiac dysfunction, and heart failure.[160] Hispanic patients were also more likely to develop heart failure compared to white patients, but no other differences between racial/ethnic groups were found. In a separate analysis of the same data by Hardy et al., all racial/ethnic groups were at an increased

risk for long-term chemotherapy (considered > 3 months) toxicity compared to white patients even after adjusting for disease stage, age, and comorbidity.[168] However, when toxic effects were evaluated among participants of a three-arm phase III trial of advanced or metastatic NSCLC, no significant differences were seen between white and black patients for any hematologic or non-hematologic adverse effects.[59] Given the uncertainty across studies, variation in the presence of previous comorbidities and the potential for differences in toxicity outcomes among racial/ethnic groups with the use of chemotherapy or targeted therapies, this is an area where additional investigation could provide useful information to clinicians regarding the safety of treatments.

2.2.3 Socioeconomic Status

2.2.3.1 Diagnosis and stage

Measures of socioeconomic status including education and income have been associated with lung cancer incidence.[34] Adults with less education, lower household income, and greater poverty have a higher incidence of lung cancer compared to adults with greater educational attainment (e.g., college), higher household income, and less poverty.[34] The elevated smoking prevalence among adults with lower socioeconomic status is a likely contributor to the higher incidence of lung cancer in this population; differences in smoking prevalence across socioeconomic groups have lessened over time, but socioeconomic status remains a significant predictor of smoking. Analysis[28] of the National Health Interview Survey (NHIS) found that Americans who had less than a high school education, were unemployed, or lived below the poverty threshold were significantly more likely to be smokers compared to individuals who at least graduated high school, were in the work force or retired, or lived above the poverty threshold.

Furthermore, an increased prevalence of smoking among adults with lower socioeconomic status may contribute to a higher rate of advanced disease observed at the time of diagnosis among this population. An evaluation of a national sample of lung cancer patients found that individuals

without medical coverage were twice as likely to present with advanced stage disease compared to individuals with health insurance.[169] Similarly, evaluation of lung cancer patients seen at a single academic medical center found that patients with indigent health care coverage were significantly more likely to present with advanced stage disease that patients with Medicare or private insurance.[35]

2.2.3.2 Treatment

Differences in the utilization of treatments within a population may be explained by socioeconomic status which is likely to be an important determinant of access to and receipt of appropriate and/or novel treatment for advanced stage NSCLC. For example, in the study by Hardy et al.,[18] patients from the lowest quartile of socioeconomic status (as measured by the percentage of individuals living below the poverty line at the census tract level) were significantly less likely than patients in the highest socioeconomic status quartile to receive chemotherapy for the treatment of stage III or IV NSCLC (OR 0.60; 95% CI 0.45, 0.79). Also, in the Davidoff et al. analysis, patients from the lowest median household income quartile and those enrolled in Medicaid or Medicare Savings Programs in the year prior to diagnosis were significantly less likely to receive any chemotherapy within 90 days of diagnosis.[15] These findings are complemented by an analysis of patients diagnosed between 2000 and 2007 with stage IV NSCLC at the University of Texas Southwestern Medical Center which found that uninsured patients (possibly reflecting lower socioeconomic status) were significantly less likely than private insured patients to receive chemotherapy even after controlling for other sociodemographic variables (OR 0.44; 95% CI 0.30, 0.64).[150] A separate analysis at the same academic medical center also found that patients of lower socioeconomic status, as measured by enrollment in an indigent health plan, were significantly less likely to receive 'standard' treatment compared to patients enrolled in Medicare or a private health insurance plan.[35]

2.2.3.3 Survival

In addition to an increased incidence of lung cancer, higher rate of advanced disease at diagnosis, and lower receipt of standard treatment, socioeconomic status has also been associated with higher mortality,[35,37] although evidence is limited and inconsistent. For example, a recent study of patients seen within the Duke Health System found that lung cancer patients residing in census tract areas of low median household income, high poverty, and low education attainment have poorer survival outcomes than patients living in census tract areas with higher median income, lower poverty, and greater education attainment.[37] Similarly, among stage I and stage II NSCLC patients seen within a single academic medical center, patients enrolled in an indigent health plan had significantly poorer survival compared to patients enrolled in Medicare or a private health plan, even after controlling for other demographic and clinical characteristics (HR 1.98, 95% CI 1.16-3.37). However, these findings are contradicted by other research[38-40] results that suggest NSCLC mortality is not associated with the socioeconomic status of patients. Thus, it is not clearly understood if and to what extent an association exists between socioeconomic status measures and lung cancer mortality.

2.2.4 Provider Affiliation

Patient access to novel treatments for lung cancer and the quality of care they receive may be influenced by where and from whom care is provided. However, limited information is available about the relationship between provider affiliations (e.g., with a teaching hospital) and the utilization of certain treatments or procedures among patients with non-small cell lung cancer. In a study using SEER-Medicare data, researchers determined that patients diagnosed with NSCLC between 1991 and 1996 were more likely to be referred to an oncology specialist if they received care at a teaching hospital.[31] In addition, among patients diagnosed with metastatic NSCLC between 1991 and 1993, those who received care at a teaching hospital were more likely to receive chemotherapy treatment compared to patients treated elsewhere.[41] The authors of this latter study also noted that the

prevalence of chemotherapy use for advanced non-small cell lung cancer was increasing, suggesting that the diffusion of newer therapies into real-world practice may occur earlier in settings such as teaching hospitals where physicians and institutions may be more likely to be exposed to or involved with the development of novel treatments.

However, community physicians and provider institutions not affiliated with a teaching hospital may still be engaged in the use of newly developed treatments through their participation in the National Cancer Institute's (NCI) Community Clinical Oncology Program (CCOP). The CCOP was designed to connect NCI Research Bases (NCI Cooperative Groups and Cancer Centers; primarily academic institutions) with a nationwide physician-based research network of community physicians to develop local clinical research infrastructures; goals of the program include patient enrollment in studies, real-world implementation of cancer treatment clinical trials, and rapid diffusion of novel evidence-based treatments into practice.[43] Thus, providers participating in the CCOP, particularly those who accrue and enroll patients in NCI treatment trials, gain access to clinical trials and research results concerning novel therapies and technological advancements that may not otherwise be accessible outside of the research network.[43] Furthermore, research suggests that CCOP-affiliated providers feel that their involvement in the provider-based research network enables them to deliver higher quality of care to their patients by keeping them updated on state-of-the-art treatment which in turn serves as an important motivating factor for their continued participation in the CCOP.[44] Indeed, research findings also support that community-based physician participation in provider-based research networks results in increased patient accrual into clinical trials and enhanced adoption of novel cancer care, ultimately characterizing an effective translation between research and clinical practice.[45-48] However, empirical evidence is still needed to support the conception of greater adoption of novel treatments among CCOP-affiliated providers within NSCLC specifically. In addition, empirical evidence is also needed to demonstrate whether treatment outcomes among NSCLC patients vary according to provider affiliation with the CCOP.

2.3 Summary of Literature Review

Non-small cell lung cancer is a common form of cancer that primarily occurs among older adults and is associated with significant morbidity and mortality. Given the asymptomatic nature of early-stage disease, most cases are diagnosed after the cancer has spread to regional lymph nodes or has metastasized to distant sites. The greater incidence of advanced disease at diagnosis contributes to the poor prognosis and bleak survival rates associated with non-small cell lung cancer, particularly among older adults who are already in poor health at the time of diagnosis. Blacks, particularly black males, are at an increased risk for developing non-small cell lung cancer and presenting with advanced stages of disease at diagnosis. In addition, blacks are less likely to receive timely, definitive and/or novel treatment despite obvious benefits and are more likely to die from non-small cell lung cancer in the United States than any other racial or ethnic group.

Platinum-based doublet chemotherapy is the standard treatment for patients with advanced stage disease and has been shown to lessen cancer-related symptoms, lengthen survival, and improve quality of life. Furthermore, previous retrospective analyses of both clinical trial and observational data have shown that the use of chemotherapy, including the use of platinum-based doublets, can improve survival among older patients. However, chemotherapy is associated with toxic adverse effects that may be especially problematic for older adults and patients with poor overall health. In some patients, the risk of toxicity may outweigh the potential benefit of treatment. Underrepresentation of older adults in cancer clinical trials and the tendency for those included being in better overall health then the general older adult population restricts the generalizability of efficacy and safety findings from clinical trials. Unfortunately, the fear of treatment toxicity and a limited amount of knowledge in the literature about the safety and efficacy of chemotherapy agents in older adults and patients with poorer performance status precludes many older patients from receiving treatment they would likely benefit from.

Efforts have been dedicated toward developing targeted treatments such as monoclonal antibodies that direct their effect toward tumor-specific characteristics, have greater activity at the cancer site and, in some cases, may result in lower systemic toxicity compared to standard chemotherapy. Bevacizumab is the only monoclonal antibody currently approved in addition to chemotherapy for the first-line treatment of advanced NSCLC in the United States. However, knowledge about the efficacy and safety of bevacizumab is limited to the results of several clinical trials. The use, safety, and effectiveness of bevacizumab in real-world practice are not well known, particularly among elderly and racial/ethnic minority patients.

The lack of knowledge about the use of bevacizumab in real-world practice, including identification of the clinical and non-clinical factors associated with its utilization, uncertainty surrounding the ability of bevacizumab to provide a survival benefit to older adults in addition to standard platinum-based doublet chemotherapy, and the concern for an increased risk of severe adverse events (especially hematologic effects) with bevacizumab warrants the need for the proposed study to evaluate the use, safety, and effectiveness of bevacizumab among older adults with advanced non-squamous non-small cell lung cancer.

2.4 Theoretical Framework

The following sections describe the theoretical framework used to guide this dissertation by illustrating the factors that contribute to the use of targeted therapies in older adults with non-small cell lung cancer and the subsequent clinical outcomes of survival and treatment-related adverse events. Andersen's Behavioral Model of Health Services Use provides the basis for the proposed theoretical framework and is described below followed by an explanation of the adaptations that were made to develop the proposed theoretical framework for the purposes of this dissertation.

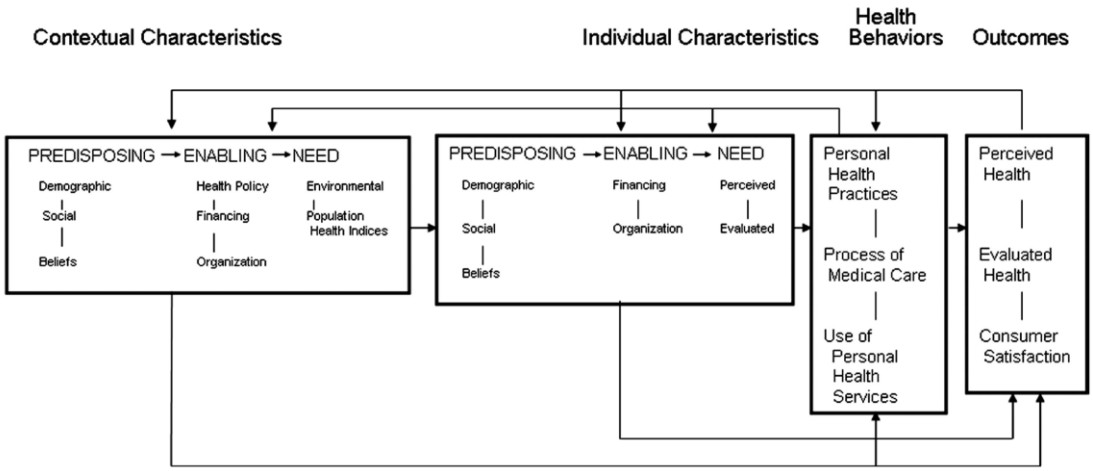
2.4.1 Andersen's Behavioral Model of Health Services Use

The first edition of Andersen's Behavioral Model of Health Services Use was developed in the late 1960s.[170] The initial model was created with the intent of providing a theoretical framework to assist in understanding families' use of health services, to define and evaluate equitable access to health care, and to facilitate the development of policies to promote equitable access.[171] The original Behavioral Model presumed that the use of health services is influenced by people's inclinations to use services, factors that promote or inhibit service use, and the need for care.[172] Furthermore, an important goal of the model was to help define and measure multiple dimensions of access to care, including potential access, realized access, equitable access, and inequitable access.[171,172]

Along with the emergence of various matters in health policy and health care delivery, new developments and ideas within health services research has led to some important additions and revisions to the Behavioral Model over the last forty years.[171] For example, in the 1970s, the health care system was explicitly included in the model to account for the influence of policies, resources, and the organizational structure of the health care system on health services use in the population. In the 1980s, a third edition of the model emerged following recognition of the important impact personal health practices such as diet and exercise have on health outcomes as well as the utility of health status as an outcome and indicator of effective or efficient health services delivery.[173,174] A fourth edition of the model was developed in the 1990s that recognized health services use as a dynamic and repetitive process; multiple factors influence health services use and subsequent health outcomes that, in turn, can affect subsequent determinants of use and health services utilization.[172] Finally, in 2007, the most recent version of the Behavioral Model was developed (Figure 2.1).[174] This latest edition delineates contextual and individual characteristics that influence health services use and also adds in the process of medical care (i.e., the interaction of providers and patients in the delivery of care services) as a component of health behavior.[171] It is the fifth edition of Andersen's

Behavioral Model of Health Services Use that serves as the backbone for the theoretical framework of this dissertation and is described in more detail below.

Figure 2.1 Andersen's Behavioral Model of Health Services Use



2.4.1.1 Contextual characteristics

Contextual characteristics refer to the circumstances and setting of health care access, involving organization, provider-related factors, and characteristics of the surrounding community.[174] These characteristics are measured at an aggregate level and individuals may be related to them through membership (e.g., health plan) or residence. Within contextual characteristics are three subcategories of determinants of health services use: predisposing characteristics, enabling characteristics, and need. Contextual predisposing characteristics, in turn, include demographic, social, and belief characteristics of the community. Demographic characteristics consist of the age, gender, and marital status arrangement within a community. Meanwhile, social characteristics include measures of education, race and ethnicity, employment rates, and crime that help to describe how the structure of a community might be supportive or detrimental to the health of its constituents and their

access to health care services. Furthermore, contextual beliefs refer to underlying community and organizational values, cultural norms, and political perspectives regarding the organization, distribution, and accessibility of health care resources in the community. However, because measures of contextual demographics and health beliefs are not available in the data source used for this study, the dissertation includes only variables that describe the social (education, race and ethnicity) constructs of the communities represented.

Contextual enabling characteristics can be broken down further into health policy, financial, and organizational characteristics.[174] Health policies can directly influence access to health care services as authoritative decisions made in both the private and public sectors. Financial characteristics, such as the rate of health insurance coverage within a community, are suggestive of the resources that are potentially available to pay for health care services; ideally, the greater the amount of financial resources per capita, the less access is inhibited because of cost or inability to pay for needed services. Organizational characteristics not only describe the amount and distribution of health care facilities and personnel that exist within a community, but also how these health care resources are structured to provide services. Measures of organizational structure include the supply of services (e.g., number of hospital beds), location, provider mix, and community outreach programs. Since this study did not intend to assess the impact of any particular health policy and the individuals included in the study were required to receive benefits through Medicare, measures of health policy and financial characteristics were not considered in the framework of this dissertation. However, organizational variables that distinguish potentially important differences between sites of care (e.g., community versus teaching hospital) were included in the conceptual model.

Contextual need variables include both environmental characteristics and population health indices.[174] Environmental need characteristics depict the physical environment of a community, such as water and air quality, that may shape the health service needs of those who reside in the area. Population health indices, on the other hand, often include rates of mortality, morbidity, and disability within a given region, and though they are typically more general than environmental need

characteristics, they are also useful in describing the need for health services within an area. Environmental characteristics are not available in the data source used for this study, however, regional variation in the prevalence and mortality rates of non-small cell lung cancer were considered in the theoretical framework.

2.4.1.2 Individual characteristics

Similar to contextual characteristics, individual characteristics also consist of predisposing, enabling, and need variables that predict and quantify health services use. The main difference between contextual and individual characteristics is the level of measurement with contextual referring to aggregate measures at a population level and individual referring to characteristics of a single person. Individual predisposing characteristics describe factors that exist prior to the onset of disease and help to predict use of health services by individuals based on their ability to identify, cope with, and utilize resources to manage health problems.[172,174] Predisposing characteristics include demographics (age, gender), social factors (race, ethnicity, occupation, social network), and personal health beliefs (attitudes, values, knowledge of health and services). However, because individual health beliefs and information about occupation and social support variables are not available in the data source used for this study, the framework of this dissertation only includes the predisposing variables of age, gender, race, and race.

Enabling characteristics of individuals refers to the resources available to individuals that can promote the use of health services.[174] More specifically, financial characteristics describe the monetary resources of income and wealth available to an individual to pay for services as well as the price of care to them based on the presence of insurance and cost-sharing responsibilities. Furthermore, organizational resources, such as a usual source of care, transportation, and travel time between residence and site of care can either facilitate or impede the use of health services. Measures of both financial (median household income) and organizational (usual source of care, distance

between residence and site of care) resources are used in the theoretical framework of this dissertation.

Need, both as perceived by an individual and as evaluated by health professionals, is the remaining component of individual characteristics that influence the use of health services.[172,174] Perceived need is a measure of how an individual views their own general health and functional state, experiences and responds to symptoms of illness, and worries about their health.[174] Individual perceptions about the significance of a health problem can ultimately lead to a decision about whether or not to seek medical care and, in turn, are useful to researchers evaluating the care-seeking process of individuals and their adherence to prescribed regimens. Evaluated need on the other hand, represents the judgment of health care professionals and/or objective measures regarding the health and functional status of an individual and the need for medical care. Thus, evaluated need characteristics often include both a diagnosis and the prognosis of particular health conditions. However, it is important to recognize that evaluated need is not always steadfast and can vary over time as clinical guidelines, prevailing practice patterns, and diffusion of innovation patterns change within the art and science of medicine. Furthermore, evaluated need is particularly useful to researchers interested in examining the types and quantities of health services being provided to individuals following initial evaluation for disease, and is an important construct in the theoretical framework of this dissertation.

2.4.1.3 Health behaviors

As depicted in Figure 2.1, both contextual and individual characteristics can influence health behaviors and health outcomes. Health behaviors are represented by the personal health practices of individuals, the process of medical care, and the actual use of personal health services. Personal health practices include measures of diet, exercise, self-care, and treatment adherence, each of which can directly affect health status as well as the need for subsequent health services. The process of

medical care involves the interaction between the provider and the patient during care delivery, and may include measures of patient counseling, prescribing patterns, and the quality of patient-provider communication.[174] Measurements of the use of health services can be general (e.g., physician office visits), as in the original Behavioral Model, or more specific to a type of service, medical condition, or provider (e.g., chemotherapy ordered by medical oncologist for non-small cell lung cancer). Although the influences of personal health practices and patient-provider communication cannot be analyzed with the data source used in this study, treatment prescribing patterns by provider specialty and the administration of chemotherapy and targeted agents were identified and used as integral components of this dissertation.

2.4.1.4 Health outcomes

Health outcomes in Andersen's Behavioral Model include both the perceived and evaluated health status of an individual; these variables are essentially the same as perceived and evaluated need characteristics as an expectation of improved access to health services is a reduction in the health service needs of an individual that were previously measured and evaluated.[174] Specifically, the perceived health status of an individual refers to the extent to which a person can function (i.e., perform activities of daily living), and live comfortably and pain-free, and is dependent on factors from other components in the model (contextual, individual, and health behavior characteristics). Evaluated health status represents the judgment of a health care professional, influenced by established clinical standards and provider experience, and involves measures similar to those of evaluated need, including functional status and prognosis. The data source used in this study does not include measures of perceived health status, and therefore, this dissertation only included measures of evaluated health status (diagnosis, survival) as outcomes.

Further, components of Andersen's Behavioral Model are useful in defining and evaluating various dimensions of access to health services.[174] For example, enabling variables measured at the

contextual and individual levels help to define potential access to care, with the idea that a greater amount of enabling resources amounts to increased likelihood for use of services. Similarly, the actual use of services represents realized access, and measures of use can be used to evaluate policies designed to have an effect on health services use. However, more important to this dissertation are the concepts of equitable and inequitable access. Both equitable and inequitable access is defined based on the characteristics that dominate the prediction of health services utilization. Although open to interpretation, traditionally, access has been defined as equitable when demographic and need variables in particular direct the greatest amount of health services use. In contrast, inequitable access results when social and enabling resources dictate which individuals receive care.

A final and relevant note about the Behavioral Model is that although predisposing, enabling, and need characteristics are all influential in determining health services use and health outcomes, the explanatory power of each component of characteristics may vary based on the type of health services being evaluated. For example, it is often expected that predisposing and need characteristics will dominate in predicting the use of hospital services because of the more serious nature of problems typically encountered in the emergency department and hospital settings.[174] Conversely, it is expected that all three components will predict the use of ambulatory services because conditions stimulating individuals to seek care in the outpatient setting are often less serious and more discretionary than those that result in inpatient treatment. Therefore, given the ambulatory nature of care for individuals in this study, it was expected that predisposing, enabling, and need variables would all factor into the use of targeted therapies among older adults with advanced non-small cell lung cancer.

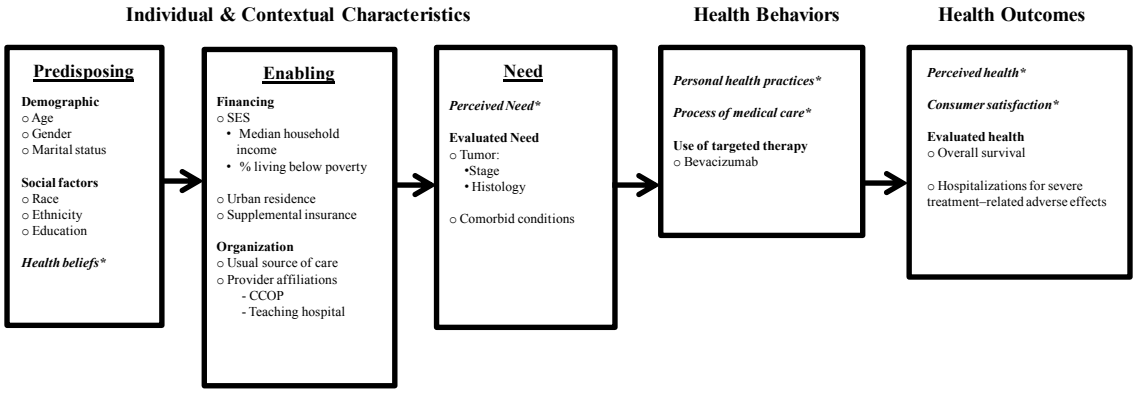
2.4.2 Proposed Conceptual Framework

The proposed conceptual framework for this study, depicted in Figure 2.2, is an adaptation to the fifth version of Andersen's Behavioral Model of Health Services Use and contains three main components: individual and contextual characteristics, health behaviors, and health outcomes.

Individual characteristics influence both health behaviors and health outcomes through the predisposing, enabling, and need attributes of individuals. Contextual characteristics are represented by predisposing, enabling, and need attributes measured at a population level; these factors affect the health behaviors and outcomes of individuals within a given community through the facilitation and promotion of health services and optimal health, or lack thereof. Health behaviors, in turn, not only influence health outcomes, but also feedback into individual and contextual characteristics that determine subsequent health services utilization. Similarly, health outcomes may affect future health behaviors of individuals and also stimulate changes to the individual and contextual determinants of subsequent health behaviors and health outcomes.

Perceived health, evaluated health, and consumer satisfaction are identified as the components of health outcomes in Andersen's Behavioral Model. However, the health outcomes of interest in this study are solely evaluated health measures (survival and hospitalization for adverse events related to the administration of bevacizumab). Furthermore, measures of patients' perceived health or satisfaction with care are not available in SEER-Medicare data and therefore are only included in the proposed framework of this study to show completeness and to identify their potential relevance as health outcomes in future studies related to treatment utilization in patients with non-small cell lung cancer. Likewise, although personal health practices and the process of medical care are components of health behaviors in Andersen's model, they are not quantifiable in the SEER-Medicare data source and therefore the utilization of bevacizumab is the sole "health behavior" measured in this study.

Figure 2.2 Proposed conceptual framework



SOURCE: Adapted from Andersen's Behavioral Model of Health Services Use[171]

2.4.2.1 Individual predisposing characteristics

Following Andersen's Behavioral Model, the individual characteristics in the proposed framework include predisposing, enabling, and need characteristics of individuals that are predictive of health services use and health outcomes. 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 (a proxy measure of socioeconomic status). Increasing age has been associated with lower receipt of local[148,175] and systemic[15] therapies for non-small cell lung cancer, as well as with poorer survival[15,176,177] and greater sensitivity to the toxic effects of systemic treatment.[160,178] Gender has also been related to differences in the receipt of timely and appropriate treatment and women tend to have improved survival[20,176,179-184] and potentially greater sensitivity to the toxic effects of treatment[179,183] compared to men.

Furthermore, marital status is another potentially important prognostic factor in lung cancer that has been associated with receipt of treatment and survival outcomes.[165,185] Arguably, marital status is an enabling factor in that marriage may afford patients the social support needed to seek out

and/or receive certain treatments that otherwise may not be made available to them. However, in this study, marital status is believed to have greater influence as a predisposing factor than as an enabling resource; marriage may enable patients to receive chemotherapy, but it predisposes individuals to seek out treatment that may prolong survival in addition to chemotherapy, such as bevacizumab. The social determinant of race has also been linked to differences in the receipt of treatment and overall survival in non-small cell lung cancer, with worse outcomes being experienced by minority patients.[17-20,22,23,25,27,58,165] Finally, the educational makeup of the community in which a patient resides is the lone quantifiable contextual predisposing characteristic. Because socioeconomic measures are not available at the individual level within the SEER-Medicare database, the census tract level measurement of education attained serves as a proxy measure of an individual's education level as well as their socioeconomic status. Indeed, previous research has shown that lower education attainment is associated with lower receipt of treatment and poorer survival outcomes among cancer patients.[186]

2.4.2.2 Enabling characteristics

State buy-in of Medicare coverage is the lone individual enabling characteristic included in the proposed framework (additional enabling characteristics are contextual and described below). State buy-in of Medicare coverage is a potentially important predictor of the use and outcomes associated with bevacizumab as state buy-in coverage has been associated with lower use of chemotherapy and poorer survival outcomes among older adults with advanced NSCLC. Contextual enabling characteristics include census tract level measure of median household income (another proxy measure of socioeconomic status), population density, provider affiliations, diagnosis year, and SEER region. Census tract level estimates of median household income have been associated with the use of chemotherapy and survival outcomes among older adults with advanced NSCLC; patients from census tract areas with lower median household income are less likely to receive chemotherapy and

have poorer survival compared to patients from census tracts with a higher median household income.[15] Furthermore, although population density was not associated with receipt of treatment or survival in previous studies of lung cancer patients,[15,187] individuals residing in rural areas may be poorer and have limited access to health care providers.[187] Characteristics of health system resources and the sites of care where patients undergo evaluation and treatment for non-small cell lung cancer can also influence what therapies are offered and received by individuals.[47] Health care providers who participate in NCI's Community Clinical Oncology Program may be more knowledgeable about and early adopters of novel therapies. In addition, provider affiliation with a teaching hospital/academic center may also influence the use of newly developed treatments. Thus, greater knowledge and earlier adoption of novel therapies by select providers may be demonstrated through an observable increase in the utilization of bevacizumab among patients with advanced NSCLC who receive treatment from providers with identifiable affiliations with provider-based research networks or academic medical centers. Furthermore, although year of diagnosis is not expected to be associated with health outcomes given the relatively short timeframe of the study, year of diagnosis is expected to have a large influence on the utilization of bevacizumab. Given that bevacizumab was approved for use in NSCLC in 2006, it is expected that utilization among older patients diagnosed in 2007 will be much greater than the rate of use seen in preceding years. Finally, the SEER region in which a patient resided at the time of diagnosis may be an important predictor of the use of bevacizumab and/or health outcomes; treatment patterns, environmental factors, and health behaviors may differ and therefore contribute to differences in the use and outcomes of bevacizumab across SEER regions.

2.4.2.3 Need characteristics

Evaluated need factors in the proposed framework include important tumor characteristics such as stage, grade, and histology, as well as the presence of comorbid conditions, hemoptysis, brain metastases, and receipt of radiation therapy and/or cancer-directed surgery. Stage and histology are

particularly important predictors of the use of bevacizumab and survival as bevacizumab is specifically indicated for the treatment of locally advanced or metastatic *non-squamous* NSCLC and has shown improved survival outcomes among patients with adenocarcinoma histology in particular.[188] Although grade is not expected to be associated with the utilization of bevacizumab, differences in tumor differentiation may influence survival outcomes among patients with poor or undifferentiated tumors likely to result in poorer survival compared to well or moderately differentiated tumors. In addition, comorbid conditions may significantly influence the need for and expected benefit from treatment among patients with NSCLC.[52,53,93,94] Similarly, the presence of hemoptysis and brain metastases are likely to affect the use of bevacizumab; patients with hemoptysis or brain metastases at diagnosis may not be good candidates for treatment with bevacizumab because of the significant increase in severe bleeding risk with its use. In addition, hemoptysis and/or brain metastases may indicate more advanced disease and worse prognosis and therefore not only influence treatment but survival outcomes.

CHAPTER THREE

METHODS

3.1 Overview of Research Design and Aims

This dissertation utilized a retrospective cohort design and the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database to evaluate the use of bevacizumab and associated outcomes in older adults diagnosed with locally advanced or metastatic non-small cell lung cancer between January 1, 2004 and December 31, 2007. Briefly, the dissertation consisted of three distinct studies aimed at identifying the utilization, safety, and effectiveness of bevacizumab use among older adults with advanced non-small cell lung cancer. Although each study addressed a separate question, the analyses are interrelated conceptually and methodologically. The first study measured the utilization of bevacizumab in combination with double agent platinum-based chemotherapy as first-line treatment for advanced non-small cell lung cancer and identified important clinical, sociodemographic, and health system characteristics that predict bevacizumab use. In particular, we were interested in whether sociodemographic variables including chronological age, race, or proxy measures of socioeconomic status explained utilization of bevacizumab after controlling for clinical factors such as tumor histology, and comorbidity. Characteristics that influenced the use of bevacizumab were evaluated in the second and third studies as potential confounders of the effect of bevacizumab on overall survival and hospitalization for severe treatment-related adverse events, respectively; confounders and other independent variables of interest were then adjusted for in the second and third studies to estimate unbiased effects of bevacizumab use on overall survival and hospitalization. The aims and a brief overview of the analyses performed are described below:

Aim 1: To describe the utilization of bevacizumab in combination with standard platinum-based doublet chemotherapy as first line treatment for older adults with advanced non-small cell lung cancer and to identify the clinical, sociodemographic, and health system factors associated with its use. In Aim 1, we first described the use of bevacizumab in older adults with advanced non-small cell lung cancer and identified bivariate associations between the use of bevacizumab and observable clinical, sociodemographic, and health system characteristics. We then estimated multivariable logistic regression models to identify characteristics that remained associated with the use of bevacizumab after controlling for other confounding variables.

Aim 2: To determine whether the use of bevacizumab in combination with standard platinum-based doublet chemotherapy as first-line treatment of older adults with advanced non-small cell lung cancer is associated with a benefit of improved overall survival. In Aim 2, we estimated the effect of bevacizumab on the probability of 1-year survival and survival duration. Unadjusted hazard ratios were generated to identify factors thought to contribute to the prediction of survival. Cox proportional hazards models were then estimated to evaluate the influence of bevacizumab on overall survival after controlling for identified risk factors. Propensity score adjustments were also utilized in the proportional hazards models to account for the confounding influence of observable characteristics associated with both treatment selection and survival.

Aim 3: To determine whether the use of bevacizumab in combination with standard platinum-based doublet chemotherapy as first-line treatment of older adults with advanced non-small cell lung cancer is associated with an increase in hospitalizations for severe treatment-related adverse events. In Aim 3, we compared the cumulative incidence of hospitalization for pre-specified adverse events (detailed below in section 3.4) among users and nonusers of bevacizumab during the first 180 days of treatment as well as within a specified window during first-line treatment. We then estimated multivariable logistic regression and Cox proportional hazards models to identify whether the association between bevacizumab and severe adverse events was independent of other factors associated with toxicities resulting in hospitalization.

3.2 Data Source

This project used the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database. Each component of the linked database is first described individually below followed by a brief description of the most current version of the SEER-Medicare database.

3.2.1 Surveillance, Epidemiology, and End Results (SEER)

The SEER Program of the National Cancer Institute (NCI) is a coordinated system of population-based cancer registries strategically distributed throughout the United States and is the only comprehensive population-based source in the country that contains data on stage at diagnosis and patient survival. Currently, the SEER Program includes data from 17 distinct registries representing approximately 28 percent of the US population, and coverage of 26 percent of blacks, 41 percent of Hispanics, 43 percent of American Indians and Alaska Natives, 54 percent of Asians, and 71 percent of Hawaiian/Pacific Islanders. SEER registries collect data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. Demographic and cancer variables are contained within a Patient Entitlement and Diagnosis Summary File (PEDSF) and include race, ethnicity, gender, marital status, date of birth, place of birth, vital status, and cause of death (provided by the National Center for Health Statistics); cancer variables include month and year of diagnosis, type of cancer, histology, grade, AJCC (American Joint Committee on Cancer) cancer stage, and initial treatment (although information may be incomplete). In addition, census tract and zip code level socioeconomic data (education, poverty, median household income) is provided in the PEDSF via the 1990 and 2000 U.S. Census.[189]

3.2.2 Medicare

Medicare is a federally funded program that provides health insurance for individuals age 65 and over as well as those under 65 with end-stage renal disease (ESRD) or certain disabilities. Among individuals in the US population aged 65 and older, approximately 97 percent are eligible to receive Medicare benefits. Nearly all Medicare beneficiaries receive Medicare Part A benefits that provide coverage for inpatient care in hospitals and use of skilled nursing facility, hospice, and some home health care services. In addition, almost all individuals who receive Medicare Part A also elect to pay a monthly premium to receive Part B benefits that provide coverage for outpatient care services including doctor visits, hospital outpatient care, durable medical equipment (e.g., blood glucose monitors), home health care, and some preventive services (e.g., flu shots). Furthermore, although most Medicare beneficiaries receive Part A and Part B benefits through traditional fee-for-service (FFS) plans administered by Medicare, some individuals opt to enroll in "Part C" or a Medicare Advantage Plan. Medicare Advantage Plans are managed care plans (similar to HMOs and PPOs) administered by private insurance companies approved by Medicare that provide coverage for all Part A and Part B eligible services. Also, Medicare Advantage Plans may offer coverage of additional services not available through the traditional Medicare FFS plan, such as prescription drugs, vision services, and health/wellness programs.

Prior to January 1, 2006, Medicare did not offer outpatient prescription drug benefits; adults aged 65 and older were reliant on other sources such as Medicaid and employer-sponsored health plans to assist them in paying for outpatient medications. Still, a large proportion of older adults did not qualify for assistance from Medicaid and over time many employers began cutting health benefits to their retirees. By 2003, nearly 1 in 4 adults aged 65 years and older lacked prescription drug coverage.[190] In order to help subsidize the costs of prescription drugs for Medicare beneficiaries, the Medicare Prescription Drug, Improvement, and Modernization Act was signed into federal law in late 2003, establishing the voluntary Medicare outpatient prescription benefit, known as Part D, that

became effective January 1, 2006. With the establishment of Part D, all Medicare beneficiaries are eligible to access the prescription drug benefit through enrollment into one of the private plans approved by the federal government, either as a stand-alone prescription drug plan (PDP) or as part of their Medicare Advantage health plan (MA-PD). Plans available to beneficiaries vary in benefit design including monthly premiums and copayment structure, medications covered, and cost-containment strategies utilized. According to 2010 estimates, approximately 60% of the 47 million Medicare beneficiaries were enrolled in a Part D plan and an additional 30% received other forms of drug coverage.[191] Furthermore, Medicare has supplanted Medicaid as the prime source of drug coverage for "dual eligible" beneficiaries (those who receive both Medicare and Medicaid benefits) and some low-income beneficiaries may also qualify for additional assistance with Part D plan premiums and cost-sharing responsibilities.

3.2.3 SEER-Medicare

The SEER-Medicare data represent a linkage of population-based tumor registry and health services use data that provide comprehensive information about Medicare beneficiaries diagnosed with cancer.[192] The linkage, first completed in 1991 and now updated biennially, is a coordinated effort between the National Cancer Institute, the SEER registries, and the Centers for Medicare and Medicaid Services (CMS). The current SEER-Medicare linkage includes all Medicare eligible persons appearing in SEER data who were diagnosed with cancer through December 31, 2007, and their Medicare claims through the end of 2009; 93 percent of adults age 65 and older appearing in SEER data files have been matched to the Medicare enrollment file. The SEER-Medicare data consist of one SEER file and several Medicare files that are described below. SEER data contain one record for each individual who has been matched between the SEER database and Medicare enrollment records; information in the SEER file includes basic demographic characteristics and diagnostic information for up to 10 identified cancers per individual. Medicare files include claims data for Part

A institutional services (MEDPAR), Part B institutional services (Outpatient Claims), services billed by individual providers under Part B (National Claims History (NCH) or Carrier Claims), home health services (HHA), hospice care, and durable medical equipment (DME). Also, as of the most recent update (early 2011), SEER-Medicare now includes yearly Part D patient enrollment information (beginning in 2006) as well as prescription drug utilization for years 2007 and 2008. The SEER-Medicare files that were available for the current study are summarized in Table 3.1; the home health services, hospice care, and Part D files were not included in the data use agreement that was made prior to the construction of this study.

There are notable limitations of the SEER-Medicare data that restrict the analyses conducted in this study. First, SEER-Medicare does not include healthcare claims information for individuals enrolled in Medicare Advantage Plans. Thus, we had to exclude patients who were covered by a Medicare Advantage Plan for any duration of time stating twelve months prior to the date of diagnosis up until the time of death or censoring given the possibility that important clinical or treatment information could be missing for these individuals. Second, SEER-Medicare also does not have information for provided services that are not billed to or covered by Medicare (e.g., services provided by Veterans Affairs, billed solely to Medicaid, or paid exclusively out-of-pocket by a beneficiary). The dependent and independent variables of interest in our study only concerned those health services covered by Medicare (e.g., hospitalization, outpatient physician visits, chemotherapy administration) so long as an individual was enrolled in Medicare Parts A and B, and although it might be possible, it seems rather unlikely that patients with continual Medicare coverage would use it to pay for some services (e.g., hospitalization) and not others (e.g., chemotherapy). However, patients with gaps in their Medicare coverage (e.g., an individual may choose not to pay for Part B while receiving benefits through Part A) may have information missing about health services they received during the time they were not enrolled in a Medicare fee-for-service plan. Therefore, we had to exclude patients who did not have continuous enrollment in both Medicare Parts A and B during the twelve months prior to the date of diagnosis through the time of death or censoring at the end of

the study period. Third, measures of patient beliefs and preferences and other potential explanatory variables that may influence the decision to use bevacizumab in advanced stage non-small cell lung cancer are absent from the SEER-Medicare data. A fourth limitation is that SEER-Medicare data does not include individual-level socioeconomic information such as household income or education attained. In an effort to get around this issue, we created a proxy measure using median household income at the census tract and zip code-levels that has been used in prior research[193,194] with SEER-Medicare data to reflect an individual patient's socioeconomic status. In addition, we paid careful attention in the assessment and interpretation of this proxy measure given the potential for misclassification of individual socioeconomic status using census tract and zip code-level information.[195] Finally, the older adults living in SEER regions are less likely to be white, live in poverty, or reside in a rural area compared to the general older adult population in the United States.[195] Therefore, we recognize that the results from this study may not be nationally representative or applicable to individuals outside of the Medicare fee-for-service population age 65 years and older who reside within the SEER regions. The remaining sections of this chapter describe cohort selection and variable measurement followed by a detailed description of the hypotheses, dependent and key independent variables, and analytical methods used in each study.

Table 3.1 Summary of SEER-Medicare data files used

Name of file	Source	Description	Variables available
Patient Entitlement and Diagnosis Summary File (PEDSF)	SEER	SEER registry and Medicare entitlement information; basic socioeconomic status variables from Census Bureau at the census tract and zip code levels	Cancer specific: month/year of diagnosis, site, stage, histology, treatment interventions within the first 4 months of diagnosis, SEER region Patient-specific: month/year of birth, date of death, gender, race, marital status, Medicare eligibility and entitlement, HMO enrollment, census tract/zip code level data on median household income, education

Table 3.1 (Continued)

Medicare Provider Analysis and Review (MEDPAR)	Medicare	Medicare Part A inpatient claims including those for skilled nursing facility use	ICD-9 diagnosis and procedure codes; date and length of stay; charges and payments made per admission
Carrier Claims (NCH)	Medicare	Medicare Part B claims from physicians and other non-institutional providers One record is created for each service provided during a visit	Date and place of service; nature of billed service using Health Care Procedure Classification Codes (HCPCS; primarily Common Procedural Terminology (CPT)-4 codes), and ICD-9 dx codes; J-codes identify specific chemotherapeutic and targeted agents administered intravenously
Outpatient Claims	Medicare	Medicare Part B claims for outpatient services from institutional providers including hospital outpatient departments; One record is created for each service provided during a visit	Date of service; beneficiary demographic information; facility provider number; ICD-9 diagnosis and procedure codes (sporadic); HCPCS J-codes to identify specific chemotherapeutic and targeted agents administered intravenously
Durable Medical Equipment (DME)	Medicare	Claims submitted to durable Medical equipment Regional carriers (DMERCs); claims for oral chemotherapies that have an intravenous equivalent	Date of service; ICD-9 diagnosis codes; HCPCS service codes; reimbursement amount; DME provider number; beneficiary demographic information

3.3 Cohort Selection

This study investigated the utilization of bevacizumab and associated health outcomes using a cohort design consisting of incident cases of locally advanced or metastatic (TNM stages IIIB and IV) non-small cell lung cancer. We excluded patients diagnosed with carcinoma in situ or stage I-IIIA as these patients are not likely to receive bevacizumab as part of their initial treatment regimen. We excluded patients with a history of cancer because prior cancer diagnoses and/or therapies may influence the use of subsequent treatments as well as survival outcomes. Similarly, patients with Medicare eligibility based on end-stage renal disease or disability were excluded as these patients are

likely to be frailer and may receive different treatment or have different treatment outcomes than the general Medicare patient population. In addition, in order to accurately identify eligible patients and account for the outcomes of interest, we excluded individuals who had information missing regarding their diagnosis or death, died within 30 days of diagnosis, were enrolled in a Medicare Advantage Plan or had any period without Medicare Parts A and B during the 12 months before or any time following diagnosis. Furthermore, to correctly identify and describe first-line treatment received by patients within the cohort, individuals who received 'other' or unspecified chemotherapy agents or received chemotherapy in an inpatient setting (i.e., in a hospital) ≤ 8 days from the date of the first chemotherapy claim were excluded. The selection of patients evaluated in this study is further described in the inclusion and exclusion criteria below.

3.3.1 Inclusion criteria

a. Patients with a primary incidence of cancer of the lung and bronchus between January 1, 2004 and December 31, 2007.
b. Patients who maintained enrollment in Medicare Parts A and B beginning 12 months prior to their diagnosis date until their date of death or censoring.
c. Patients who received chemotherapy ≤ 120 days from the date of diagnosis.
d. Patients who received initial chemotherapy consisting of the administration of a platinum and non-platinum chemotherapy agent ≤ 8 days from the first date of chemotherapy.

3.3.2 Exclusion criteria

a. Patients with a prior or simultaneous diagnosis of other cancer.
b. Patients with missing or invalid data for the date of diagnosis.
c. Patients diagnosed prior to their 66th birthday.
d. Patients diagnosed at the time of death or autopsy.

e. Patients originally entitled to Medicare due to end-stage renal disease or disability.

f. Patients enrolled in a Medicare Advantage Plan during the 12 months before or any time following diagnosis.

g. Patients diagnosed with carcinoma in situ, stage I – IIIA, or stage unknown.

h. Patients diagnosed with tumors of unknown histology or not of non-small cell histology.

i. Patients diagnosed with squamous cell tumors. Bevacizumab is only indicated for use in patients with tumors of non-squamous histology; squamous histology is associated with a significant increased risk for bleeding complications with use of bevacizumab.[196]

j. Patients whose date of death was ≤ 30 days from the date of diagnosis.

k. Patients who received 'other' or unspecified chemotherapy agents or received chemotherapy in an inpatient setting (i.e., in a hospital) ≤ 8 days from the date of first chemotherapy claim.

3.4 Measurement of Variables

This section describes how the clinical, sociodemographic, and health system characteristics, identified by clinical theory and previous literature as potential factors in the utilization and outcomes of bevacizumab treatment, were measured using SEER-Medicare data. Operationalization of the dependent variables, key independent variables, and additional covariates used in the analyses are detailed in text and summarized in Tables 3.2, 3.3, and 3.4 below.

3.4.1 Dependent variables

- **Use of bevacizumab:** Use of bevacizumab was the dependent variable of interest in the first study and the main exposure (independent variable) of interest in the second and third studies. Use of bevacizumab was measured through identification of claims from NCH (provider) and

outpatient facility files with the HCPCS code for bevacizumab administration, J9035. A dichotomous variable was created to indicate any or no use of bevacizumab; an individual patient was considered a user of bevacizumab if at least one claim with code J9035 was present following diagnosis and occurred within 8 days of the start of the initial chemotherapy regimen (i.e., the 'treatment identification window'). A separate dichotomous variable was also created to identify whether or not patients had at least one claim for bevacizumab present within the first 30 days of chemotherapy treatment. Several additional variables were created to more completely illustrate the use of bevacizumab including the time (in days) between diagnosis and bevacizumab initiation, total duration (in months) of bevacizumab use, and the total number of bevacizumab cycles (administrations). Given that SEER only provides the month and year of diagnosis, we created an artificial date of diagnosis using the 1st day of the diagnosis month in order to measure the number of days between the date of diagnosis and the date bevacizumab was first administered.

- **Overall survival:** Overall survival, a measure of the benefit of bevacizumab and a major outcome of interest, was evaluated using two separate measures. The first measure was the probability of 1-year overall survival. Follow-up time started on the first date of chemotherapy and/or bevacizumab administration, whichever occurred earlier. Patients were followed daily until the date of death or until the date of one year was reached. A dichotomous variable, one-year survival (yes/no), was created to indicate whether or not a patient survived one-year following the initiation of treatment. The second measure, overall survival duration, also started from the time of treatment initiation and followed the survival of patients daily until the date of death or date of censoring (loss to follow-up or end of study period), whichever occurred earlier. A continuous variable, time-to-event (death), was created to indicate the number of days a patient survived, calculated as the date of death minus the date treatment was initiated. To assess for the possibility of immortal time bias, follow-up

time in a sensitivity analysis was initiated on the first day following the treatment identification window. Thus, when the utilization of treatment was assessed over the first 8 days of chemotherapy, follow-up began on the 9th day of treatment; when utilization was assessed over the first 30 days of chemotherapy, follow-up began on the 31st day of treatment.

- **Hospitalization for severe treatment-related adverse events:** Hospitalizations for severe adverse events previously evaluated and/or associated with bevacizumab,[197] including arterial thromboembolic events, neutropenia, gastrointestinal perforation, and severe hemorrhage were identified using hospitalization claims from the MEDPAR (inpatient) file. Claims from the MEDPAR file were evaluated beginning on the date of first chemotherapy or bevacizumab administration, whichever came earlier. Hospitalizations for severe adverse events were assessed over the first 180 days following the initiation of treatment as well as during a specified first-line treatment window. These measures are described separately below:

  Hospitalization during the first 180 days of treatment: Hospitalizations for specific severe adverse events were considered to have occurred during the first 180 days of treatment if within that time period an inpatient service claim was present and contained at least one of the ICD-9 or CPT codes included in Table A-1 of Appendix A. Follow-up time started on the date of treatment initiation (day 1) and followed patients daily until the date of hospitalization or day 180, whichever occurred first. A dichotomous variable (yes/no) was created to indicate whether or not the patient was ever hospitalized for each of the specified adverse events during the first 180 days of treatment.

  Hospitalization during first-line treatment window: The first-line treatment window was defined as the duration of time between the date initial treatment started to the earlier of two possible endpoints: 1) the date of cessation of first-line treatment + 30 days or 2) the date a

new treatment agent was initiated, where 'new treatment' refers to any agent not previously administered within the 8-day treatment identification window. Because patients were treated with multiple agents that may have been administered and/or stopped at different points in time, the 'date of cessation of first-line treatment' was considered the earliest time point that a final claim for any of the first-line agents was identified. Hospitalizations were considered due to specific treatment-related adverse events if they occurred during the first-line treatment window and the inpatient service claims contained at least one of the ICD-9 diagnosis codes included in Table A-1 of Appendix A. Follow-up time started on the date of treatment initiation and followed patients daily until the date of hospitalization or the end of the first-line treatment window, whichever occurred first. A dichotomous variable, treatment-related hospitalization (yes/no), was created to indicate whether or not a patient was ever hospitalized for each of the adverse events of interest during the first-line treatment window. In addition, a continuous variable, time-to-event (hospitalization), was created to indicate the number of days a patient was free from hospitalization for the specific treatment-related adverse events, measured as the as the date of hospitalization minus the date treatment was initiated.

Table 3.2 Summary of dependent variables

Aim	Variable description	Type	Source File	Definition
Aim 1	Use of bevacizumab	Dichotomous	Medicare NCH & Outpatient	Use of bevacizumab within 8 days from the first claim date for chemotherapy
Aim 2	One-year survival	Dichotomous	PEDSF; Medicare NCH & Outpatient	Survival one-year from the first claim date for chemotherapy and/or bevacizumab (whichever occurred first)
	Time-to-event (death)	Continuous	PEDSF; Medicare NCH & Outpatient	Time in days from the first claim date for chemotherapy and/or bevacizumab (whichever occurred first) to date of death; patients censored at date lost to follow-up or end of the study
Aim 3	Treatment-related hospitalization (180 days)	Dichotomous	MEDPAR	Hospitalization for arterial thromboembolic events, gastrointestinal perforation, neutropenia, or severe hemorrhage between the first claim date for chemotherapy and/or bevacizumab (whichever occurred first) and day 180 of treatment
	Treatment-related hospitalization (first-line treatment window)	Dichotomous	MEDPAR	Hospitalization for arterial thromboembolic events, gastrointestinal perforation, neutropenia, or severe hemorrhage between the first claim date for chemotherapy and/or bevacizumab (whichever occurred first) and the cessation of first-line treatment
	Time-to-event (hospitalization during first-line treatment window)	Continuous	MEDPAR	Time in days from the first claim for chemotherapy and/or bevacizumab (whichever first) to date of hospitalization for specified adverse event; patients censored at date of death or end of the study

3.4.2 Key independent variables

- **Age:** Age was specified as both a continuous variable and a categorical variable to classify patients into different age groups. Age was classified in 2 different ways: into 3 distinct groups, 66-69, 70-79, and 80+ and into 2 distinct groups, 66-69 and 70+. Age was calculated

by subtracting the month and year of birth from the month and year of diagnosis in the PEDSF file.

- **Race:** Race was identified in the PEDSF file and categorized as white, black, other (representing patients not identified as being of white or black race). Race information is available from both SEER and Medicare data, and there is a high degree of correlation between the two sources for both blacks and whites.[195] However, there is less certainty in identifying non-white and non-black race groups within either of the two data sources. In addition, because of the lower incidence of lung cancer among individuals of non-white/non-black race, we chose not to further categorize other racial groups. Similarly, because of the lower incidence of lung cancer among individuals of Hispanic ethnicity and the concern for small sample sizes, Hispanic ethnicity was not operationalized or evaluated in the current study.

- **Socioeconomic status:** Direct measurement of an individual's socioeconomic status is not possible using SEER-Medicare data; information for socioeconomic variables such as median household income and education are not provided at the individual level. However, SEER-Medicare does provide aggregate data for median household income and education attainment at the 2000 National Census Tract and zip code-levels in the PEDSF file, and this information can be used to create a proxy measure for socioeconomic status.[195] We used census tract-level information on the percentage of individuals aged 25 and older with less than a high school education to rank patients into quartiles of education attainment. In addition, we used census-tract information to rank patients into quartiles of median household income overall.

- **Provider affiliation with CCOP:** Provider affiliation with NCI's CCOP can be obtained from the semi-annual publication of CCOP Progress Reports. We linked provider CCOP

affiliation information to SEER-Medicare claim files (NCH and Outpatient) via the unique provider identification number (UPIN) or the NPI number of each provider (starting 07/01/2007). Patients were considered to have received treatment from a CCOP-affiliated provider if at least 50% of their identified chemotherapy claims were from a provider (NCH or Outpatient) affiliated with CCOP. Because UPIN and NPI information is normally encrypted within SEER-Medicare data, special permission was granted during the data application process in order to obtain unencrypted UPIN and NPI numbers within the SEER-Medicare claims files.

Table 3.3 Summary of key independent variables

Variable	Type	Source File	Definition
Age	Continuous & Categorical	PEDSF	Categorized as: 66-69; 70-79; and 80+
Race	Categorical	PEDSF	White; Black; Other
Table 3.3 (continued) Median household income	Categorical	PEDSF	Aggregate census tract level measure of median household income
Percent 25 and older with < high school education	Categorical	PEDSF	Aggregate census tract level measure of education attainment
Receipt of treatment from a CCOP-affiliated provider	Dichotomous	CCOP progress reports linked to Medicare NCH & Outpatient claims files	Receipt of treatment from a provider affiliated with the National Cancer Institute's Clinical Community Oncology Program

3.4.3 Additional covariates

3.4.3.1 Additional predisposing characteristics

- **Sex:** Information on patient sex was provided in the PEDSF file and categorized as 'male' or 'female'.

- **Marital status:** Information on marital status at the time of diagnosis was provided in the PEDSF file. We categorized marital status as 'married' and 'not married' which included all patients who were single, separated, divorced, or widowed at the time they were diagnosed.

3.4.3.2 Additional enabling characteristics

- **Medicaid coverage preceding diagnosis:** The PEDSF file provides the number of months of state buy-in (Medicaid) coverage in each year a patient is eligible for Medicare. However, since the actual months in which state buy-in coverage occurred during the year are not available, it may not be possible to determine whether Medicaid coverage preceded diagnosis. Therefore, we determined that a patient had Medicaid coverage preceding diagnosis if information from the PEDSF file indicated one or more months of state buy-in coverage during the calendar year prior to diagnosis (e.g., if a patient was diagnosed in any month of 2006, we looked in 2005 for state buy-in coverage). A dichotomous variable (yes/no) was created to indicate whether or not a patient had any state buy-in coverage during the calendar year preceding diagnosis.

- **Population density:** The PEDSF file includes Rural/Urban Continuum Codes from the Economic Research Service of the Department of Agriculture that are used to distinguish metropolitan and nonmetropolitan counties. The Rural/Urban Continuum Codes categorize metropolitan counties into 3 groups based on population size (e.g., metro area w/ population

of 1 million or more; metro area w/ population between 250,000 and 1 million; metro area w/ population less than 250,000) and nonmetropolitan counties into 6 groups based on urbanization and adjacency to a metro area (e.g., urban w/ 20,000 or more and adjacent to metro area; urban population of 20,000 or more, not adjacent to metro area; urban population of 2,500 to 19,999, adjacent to metro area; urban population of 2,500 to 19,999, not adjacent to metro area; rural or urban population less than 2,500, adjacent to metro area; rural or urban population less than 2,500, not adjacent to metro area).To avoid small cell sizes and to simplify statistical comparisons we combined similar groups. We combined the 3 metropolitan groups to form the metropolitan statistical area (MSA) category, and we combined the 4 urban groups and the 2 rural groups to form the urban/rural category.

- **Additional provider affiliations:** The SEER-Medicare Provider file contains information about the characteristics of physicians and hospitals that provide care to patients, including affiliation with cooperative research groups (e.g., 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 directly to MEDPAR and Outpatient file claims using an encrypted provider identification number. We used this linkage to identify whether or not patients received care from providers with the aforementioned affiliations. We defined care at an affiliated site as at least one chemotherapy and/or bevacizumab claim from a provider with the designated affiliation. An indicator variable was created for each distinct affiliation (cooperative research group, NCI cancer center, teaching hospital, medical school) to denote whether a patient received treatment from an affiliated provider.

- **Diagnosis year:** We operationalized the year a patient was diagnosed to capture time trends in the use of and outcomes associated with bevacizumab. We created a categorical variable to indicate which of the four years (i.e., 2004, 2005, 2006, or 2007) a patient was diagnosed in.

Due to the likelihood of low utilization of bevacizumab prior to the calendar year in which it received approval for NSCLC (2006), we combined years 2004 and 2005 into one category.

- **SEER Region:** We operationalized the SEER region in which a patient was diagnosed to capture geographical trends in the use and outcomes of bevacizumab. SEER registries were categorized by state/region as follows: East = Connecticut and New Jersey; Midwest = Iowa, Michigan, New Mexico, and Utah; South = Georgia, Kentucky, and Louisiana; West = California, Hawaii, and Washington.

3.4.3.3 Need characteristics

- **Stage:** The PEDSF file provides tumor stage information (based on AJCC 6th edition tumor staging guidelines) which we operationalized as a potential prognostic factor. We categorized patients into two distinct staging groups: Stage IIIB and Stage IV disease. In addition, PEDSF also provides a summary stage variable that we used as a secondary staging variable and categorized patients as having regional or distant stage disease.

- **Grade:** The PEDSF file provides tumor grade information which we operationalized into three categories: Well/moderately differentiated, poor/undifferentiated, and unknown.

- **Histology:** We used the ICD-O-3 morphology codes within the PEDSF file to identify histology type. Histology was then categorized as adenocarcinoma, large cell, or other/not otherwise specified (NOS). Adenocarcinoma included the following ICD-O-3 codes: 8140-8147, 8250-8255, 8260, 8310, 8320, 8323, 8350, 8430, 8460, 8480-8481, 8490, 8507, 8510, 8550-8551, 8560, 8562, and 8570-8576. Large cell included the following ICD-O-3 codes: 8012-8015. Other/NOS included the following ICD-O-3 codes: 8020-8022, 8030-8035, 8046, and 8050, 8200-8201, 8230-8231, 8240-8246, 8249, and 8980. Patients with histology codes for squamous tumors (ICD-O-3 codes 8051-8078, 8083-8084, and 8123) or other ICD-O-3

codes not representative of non-squamous NSCLC (ICD-O-3 codes 8000-8011, 8041-8045, 8580, 8720, and any code >= 8800) were excluded from the study.

- **NCI Charlson comorbidity index score:** The Charlson index[198] is a measure of disease burden commonly used in health services and outcomes research as a proxy for health status. The index has been adapted[199-201] to utilize ICD-9 coded data from administrative databases and has since been validated as a reliable tool to predict mortality in cancer patients.[202-204] We measured patient comorbidity during the 12 months prior to diagnosis using a variation[203] of the Charlson index designed specifically for research of breast, prostate, colorectal, and lung cancers using administrative claims data; NCI provides a statistical macro[205] for this version of the Charlson index that uses physician and hospital claims (from MEDPAR, NCH, and Outpatient files) as well as cancer site-specific weights for the following comorbidities: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, dementia, paralysis, diabetes, diabetes with sequelae, chronic renal failure, moderate or severe liver disease, ulcers, rheumatic disease, and AIDS. Index scores were categorized in accordance with previous research[15] as no comorbidities, one comorbidity, two comorbidities, or three or more comorbidities. In addition, we evaluated for the presence of specific comorbidities (e.g., thromboembolic disorders) that may influence whether or not patients received bevacizumab (i.e., they may increase the risk of treatment-related complications).

- **Hemoptysis:** The presence of hemoptysis can be a contraindication to the use of bevacizumab, although this may depend on the severity and amount of blood being produced upon coughing. We evaluated MEDPAR, NCH, and Outpatient files for the presence of ICD-9 diagnosis codes (786.3, 786.30, and 786.39) that may be indicative of hemoptysis in medical claims prior to and at the time of diagnosis in order to get a sense of how the presence of hemoptysis may be related to the use of bevacizumab. We created an indicator

variable to denote whether a patient was identified as having a diagnosis for hemoptysis prior to or at the time of diagnosis (time of diagnosis is arbitrarily chose as the first day of the diagnosis month since we do not know the actual date of diagnosis).

- **Brain metastases:** The presence of brain metastases can indicate signs of advanced disease and may influence the use of bevacizumab, particularly if there is concern for intracranial bleeding. We evaluated MEDPAR, NCH, and Outpatient files for the presence of ICD-9 diagnosis code (198.3) that may be indicative of brain metastases prior to and at the time of diagnosis to get a sense of how the presence of brain metastases may be related to the use of bevacizumab. We created an indicator variable to denote whether a patient was identified as having a diagnosis code for brain metastases present in their claims history prior to or at the time of diagnosis.

- **Receipt of radiation:** Receipt of radiation may be an indicator of disease severity and/or prognosis and therefore may influence the use of bevacizumab. PEDSF contains information about radiation and surgery and whether those modalities are used as part of the first course of treatment. We evaluated the PEDSF file and created an indicator variable to denote whether or not patients received radiation therapy during the first course of treatment.

- **Cancer-directed surgery:** Receipt of cancer-directed surgery may be an indicator of disease severity and/or prognosis and therefore may influence the use of bevacizumab. PEDSF contains information about radiation and surgery and whether those modalities are used as part of the first course of treatment. We evaluated the PEDSF file and created an indicator variable to denote whether or not patients received cancer-directed surgery during the first course of treatment. Due to possible sample size issues, we did not investigate into the distinct types of surgical procedures that may have been performed.

Table 3.4 Summary of additional covariates

Variable	Type	Source File	Categorization
Sex	Dichotomous	PEDSF	Male; Female
Marital status	Dichotomous	PEDSF	Married; Not married (single, separated, widowed, divorced)
Population density	Dichotomous	PEDSF	Metropolitan statistical area; Urban/rural
State buy-in Medicare coverage during year preceding diagnosis	Dichotomous	PEDSF	Yes; No
Provider affiliations			
Cooperative research group	Dichotomous	Provider	Yes; No
NCI designated cancer center	Dichotomous	Provider	Yes; No
Teaching hospital	Dichotomous	Provider	Yes; No
Medical school	Dichotomous	Provider	Yes; No
Year of diagnosis	Categorical	PEDSF	2004-2005, 2006, 2007
SEER region	Categorical	PEDSF	East = CT, NJ; Midwest = IA, MI, NM, UT; South = GA, KY, LA; West = CA, HI, WA
AJCC tumor stage	Dichotomous	PEDSF	Stage IIIB; Stage IV
Summary stage	Dichotomous	PEDSF	Distant stage; Regional stage
Grade	Categorical	PEDSF	Well/moderately differentiated; Poor/undifferentiated; Unknown
Tumor histology	Categorical	PEDSF	Adenocarcinoma; Large cell; Other/not otherwise specified
NCI Charlson comorbidity index	Categorical	MEDPAR, NCH, & Outpatient	0; 1; 2
Hemoptysis	Dichotomous	MEDPAR, NCH, & Outpatient	Yes; No
Brain metastases	Dichotomous	MEDPAR, NCH, & Outpatient	Yes; No
Radiation therapy	Dichotomous	PEDSF	Yes; No
Cancer-directed surgery	Dichotomous	PEDSF	Yes; No

3.4.3.4 Other characteristics

- **Time to treatment initiation:** We measured time to treatment initiation as a potential prognostic indicator that could mediate the effects of treatment on survival outcomes. Using Medicare NCH and Outpatient file claims, we created a continuous variable, 'time to treatment start', to identify and measure the time in days between the date of diagnosis and the first date initial treatment was administered; the date of the first claim for either chemotherapy or bevacizumab administration, whichever occurred first, was used as the first date of initial treatment. Given that SEER only provides the month and year of diagnosis, we created an artificial date of diagnosis using the 1st day of the diagnosis month in order to measure the number of days between the date of diagnosis and the date treatment was first administered.

- **Chemotherapy regimen:** We were interested in describing the use of other chemotherapy agents as first-line treatment to better illustrate the overall treatment patterns of older adults with advanced non-squamous non-small cell lung cancer and to describe the use of bevacizumab in a larger context. We used Medicare NCH and Outpatient file claims to identify the administration of specific chemotherapy agents by HCPCS J-code. The specific chemotherapy agents and their respective HCPCS J-codes are listed in Table 3.5. Beginning with the date of the first chemotherapy claim, we captured the use of any chemotherapeutic agents within the first 8 days of chemotherapy to determine the specific treatment regimen utilized. Patients without one claim for a platinum agent and one claim for a non-platinum agent during the 8-day treatment identification period were excluded from the original analysis as were individuals with claims for more than two chemotherapeutic agents during this period. We created a dichotomous variable, platinum-doublet, to indicate whether a platinum-based doublet was administered as first-line treatment. Similarly, to analyze a more specific subgroup of patients, we created an additional dichotomous variable, platinum-

taxane, to indicate whether a platinum-taxane regimen was administered as first-line treatment. We also created dichotomous variables (yes/no) to indicate the use of each specific chemotherapy agent as part of our descriptive analysis.

Table 3.5 HCPCS J-codes for chemotherapeutic agents and bevacizumab

Drug Class	Therapeutic Agent	HCPCS J-code
Monoclonal antibody	Bevacizumab	J9035
Platinum-coordination complex	Carboplatin	J9045
	Cisplatin	J9060, 9062
	Oxaliplatin	J9263
Taxane	Docetaxel	J9170
	Paclitaxel	J9264, 9265
Folic acid antagonist	Pemetrexed	J9305
DNA topoisomerase inhibitor	Irinotecan	J9206
	Topotecan	J9350
Alkylating agent	Cyclophosphamide	J9070, 9080, 9090-9097
Pyrimidine analog	Fluorouracil	J9190
	Gemcitabine	J9201
Vinca alkaloid	Vinblastine	J9360
	Vincristine	J9370, 9375, 9380
	Vinorelbine	J9390

3.5 Study Design and Methods

3.5.1 Aim 1

To describe the utilization of bevacizumab in combination with standard platinum-based doublet chemotherapy as first line treatment for older adults with advanced non-small cell lung cancer and to identify the clinical, sociodemographic, and health system factors associated with its use. The *a priori* hypotheses for this study are as follows:

H1: Among older adults with a primary diagnosis of advanced non-squamous non-small cell lung cancer, non-white patients are significantly less likely than white patients to receive bevacizumab in combination with standard platinum-based doublet chemotherapy.

H2: Among older adults with advanced non-small cell lung cancer, patients of lower socioeconomic status are significantly less likely than patients of higher socioeconomic status to receive bevacizumab in combination with standard platinum-based doublet chemotherapy.

H3: Among older adults with advanced non-small cell lung cancer, patients 70 years or older are significantly less likely than patients 66 to 69 years of age to receive bevacizumab in combination with standard platinum-based doublet chemotherapy.

H4: Among older adults with advanced non-small cell lung cancer, patients who receive treatment from a provider affiliated with the National Cancer Institute (NCI) Community Clinical Oncology Program (CCOP) are significantly more likely to receive bevacizumab in combination with standard platinum-based doublet chemotherapy compared to patients who receive treatment from non-CCOP-affiliated providers.

3.5.1.1 Study population

This aim investigated the utilization of bevacizumab and factors associated with its use among incident cases of locally advanced or metastatic (TNM stages IIIB and IV) non-small cell lung cancer in older adults. Patients with a history of cancer were excluded because prior cancer diagnoses and/or therapies may influence the use of subsequent treatments. Similarly, patients with Medicare eligibility based on end-stage renal disease or disability were excluded as these patients are likely to be frailer and may receive different treatment or have different treatment outcomes than the general Medicare patient population. In addition, in order to accurately identify patients who were eligible to receive bevacizumab and detect relationships between bevacizumab use and the patient and health system characteristics of interest, we excluded individuals who were: diagnosed prior to reaching 66

years of age, diagnosed at death or autopsy, deceased within 30 days of diagnosis, missing any information about their diagnosis or death, diagnosed with squamous cell NSCLC (contraindication for bevacizumab), diagnosed with carcinoma in situ or stage I through stage IIIA, missing any information about their tumor stage or histology, enrolled in a Medicare Advantage Plan or had any period without Medicare Parts A and B during the 12 months before or any time following diagnosis. Furthermore, to correctly identify and describe first-line treatment received by patients within the cohort, individuals who received 'other' or unspecified chemotherapy agents or received chemotherapy in an inpatient setting (i.e., in a hospital) ≤ 8 days from the date of the first chemotherapy claim were excluded.

3.5.1.2 Dependent and key independent variables

- The dependent variable of interest in this aim was the addition of bevacizumab to platinum-based doublet chemotherapy for the first-line treatment of older adults with locally-advanced or metastatic non-small cell lung cancer. Given that a main objective of this study was to identify the proportion of older adults with advanced NSCLC who received bevacizumab, we created a simple indicator variable to indicate whether or not bevacizumab was used within 8 days from the date of first chemotherapy treatment (yes/no). Additionally, a second indicator variable to indicate whether bevacizumab was added to first-line chemotherapy with 30 days from the date of first chemotherapy treatment was created for purposes of a sensitivity analysis. Also, in an effort to more completely capture and describe how bevacizumab was utilized in this cohort, we also measured a few additional aspects of bevacizumab use: time to bevacizumab start, duration of use, and the number of administrations.

- Key independent variables of interest in this aim included age, race, census tract-level information on median household income and education attainment (proxy measures of socioeconomic status), as well as receipt of treatment from a CCOP-affiliated provider.

3.5.1.3 Control variables

- Control variables considered in this aim included gender, marital status at the time of diagnosis, Medicaid coverage preceding diagnosis, population density, year of diagnosis, SEER region, tumor stage, grade, and histology, NCI Charlson comorbidity index score, presence of brain metastases, presence of hemoptysis, receipt of radiation treatment, and receipt of cancer-directed surgery.

3.5.1.4 Methods of analysis

In our analysis, we first described patients with respect to demographic, clinical, and health system characteristics both overall and stratified by first-line bevacizumab use in order to identify potential underlying differences between those who received bevacizumab and those who did not. Analyses were further stratified by the two cohorts used in the overall study: 1) the larger cohort of patients receiving any platinum-based doublet chemotherapy and 2) the smaller cohort of patients who specifically received doublet chemotherapy consisting of a platinum agent and a taxane agent. Frequencies with chi-square tests of significance and t-tests were used to compare differences in patients by bevacizumab use across important clinical and sociodemographic variables including age, race, census tract level measures for education and median household income, receipt of treatment from a CCOP-affiliated provider, tumor stage, grade, and histology, as well as NCI Charlson comorbidity index score. Multivariable logistic regression was then used to model the use of bevacizumab and estimate the relative impact of each of the key independent variables on the odds of bevacizumab use while controlling for the other covariates in the model. Multicollinearity between covariates was assessed prior to constructing the regression models by examining variance inflation factors and tolerance values.[216] The Hosmer-Lemeshow goodness of fit test[216] was used to determine whether each regression model adequately fit the data. Goodness of fit statistics including the LRT

and the Akaike Information Criterion (AIC) were used to compare and eventually select the final regression models. Additionally, hierarchical logistic regression was performed based on the conceptualization of Andersen's Behavioral Model of Health Services Use. Initially, a logistic regression model of the use of bevacizumab was fit with the predisposing characteristics included as covariates, regardless of their significance in bivariate analyses. Subsequent models were created in a hierarchical fashion by first adding in enabling characteristics as covariates followed by the inclusion of need characteristics to create a third model. The idea behind this analysis was to assess how identified associations between the use of bevacizumab and important predisposing factors such as age and race are modified (if at all) when additional characteristics are successively accounted for in the regression models.

3.5.2 Aim 2

To determine whether the use of bevacizumab in combination with standard platinum-based doublet chemotherapy as first-line treatment of older adults with advanced non-small cell lung cancer is associated with a benefit of improved overall survival. The *a priori* hypotheses for this study are as follows:

H5: Among older adults with advanced non-small cell lung cancer, patients who receive bevacizumab in combination with standard platinum-based doublet chemotherapy as first line treatment do not have significantly improved overall survival compared to patients receiving standard platinum-based doublet chemotherapy only.

3.5.2.1 Study population

This aim investigated the potential benefit of bevacizumab use on overall survival among incident cases of locally advanced or metastatic (TNM stages IIIB and IV) non-small cell lung cancer in older adults. Patients with a history of cancer were excluded because prior cancer diagnoses and/or

therapies may influence the use of subsequent treatments. Similarly, patients with Medicare eligibility based on end-stage renal disease or disability were excluded as these patients are likely to be frailer and may receive different treatment or have different treatment outcomes than the general Medicare patient population. In addition, in order to accurately identify patients who were eligible to receive bevacizumab and detect relationships between bevacizumab use and the patient and health system characteristics of interest, we excluded individuals who were: diagnosed prior to reaching 66 years of age, diagnosed at death or autopsy, deceased within 30 days of diagnosis, missing any information about their diagnosis or death, diagnosed with squamous cell NSCLC (contraindication for bevacizumab), diagnosed with carcinoma in situ or stage I through stage IIIA, missing any information about their tumor stage or histology, enrolled in a Medicare Advantage Plan or had any period without Medicare Parts A and B during the 12 months before or any time following diagnosis. Furthermore, to correctly identify and describe first-line treatment received by patients within the cohort, individuals who received 'other' or unspecified chemotherapy agents or received chemotherapy in an inpatient setting (i.e., in a hospital) ≤ 8 days from the date of the first chemotherapy claim were excluded.

3.5.2.2 Dependent and key independent variables

- The dependent variable in this aim was the time to event (overall survival) as measured in the number of days between the start of treatment until the time the event occurred (death or censoring); analysis of time to event included both one-year survival and survival duration. For survival duration, patients who did not experience the event (death) were censored at the end of study date. A second measurement of time to event was created for use in a sensitivity analysis where the beginning of follow-up started on the first day following the treatment identification window. That is, when the first 8 days of treatment were used to identify

chemotherapy regimen and bevacizumab use, follow-up time started on day 9; when the first 30 days of treatment were used in a sensitivity analysis, follow-up time started on day 31.

- The key independent variable of interest in this aim was the use of bevacizumab within 8 days of the start of first-line treatment with standard platinum-based doublet chemotherapy.

3.5.2.3 Control variables

- Control variables considered in this aim included clinical and sociodemographic characteristics that could influence overall survival and may also have been associated with the use of bevacizumab in the first study (confounders): age, race, census tract-level information on median household income and education attainment (proxy measures of socioeconomic status), receipt of treatment from a CCOP-affiliated provider, sex, marital status at the time of diagnosis, Medicaid coverage preceding diagnosis, population density, NCI Charlson comorbidity index score, year of diagnosis, SEER region, and tumor stage, grade, and histology.

3.5.2.4 Methods of analysis

We conducted analyses of one-year survival and survival duration using an intent-to-treat approach with survival attributed to the treatment regimen the patient was first initiated on following diagnosis. Our primary analysis concerned the potential benefit in overall survival with the addition of bevacizumab to platinum-based doublet chemotherapy as first line treatment. Therefore, our main comparison contrasted overall survival between patients who received bevacizumab in addition to platinum-based doublet chemotherapy with those patients who received platinum-based doublet chemotherapy only. Additionally, we also evaluated the effect of bevacizumab on overall survival among patients who were treated first-line with platinum-taxane regimens specifically.

Logistic regression was used to estimate the odds of death at one year following the start of treatment, comparing patients who received bevacizumab with those patients who did not. Bivariate analyses of each independent variable with one-year survival were performed followed by multiple logistic regressions that incorporated the covariates associated with survival. Interaction terms between bevacizumab use and demographic, clinical, and site of care variables were evaluated for inclusion in the final regression models using the log likelihood ratio test (LRT); the intent of the interaction terms was to identify those covariates that modified the survival effect of bevacizumab treatment.

For survival duration, we first conducted bivariate analyses using Kaplan-Meier survival curves for bevacizumab as well as each of the categorical covariates of interest to provide insight into the shape of the survival function and determine visually whether the survival functions of comparator groups were approximately parallel. Other descriptive statistics were also generated including the proportion of patients censored and median of time to the event (death). In addition, we used long-rank tests to measure equality across the strata of each categorical variable and determine whether or not the variable should be considered for inclusion in the multivariable Cox proportional hazard models. For continuous variables we used bivariate Cox proportional hazard regression. Covariates were considered for inclusion in the final multivariable models if they had a significant association with survival at a p-value of 0.05 or less or they were considered to be clinically relevant.

Cox proportional hazard (PH) models were used to estimate the independent relationship between bevacizumab use and overall survival duration after controlling for independent variables associated with survival. The Cox PH model is a semi-parametric model that allows for the inclusion of multiple predictor variables and provides a partial likelihood estimation of the hazard of an event, such as death. Both continuous and categorical variables can be included in the model and selection of a probability distribution for the outcome of interest (death) is not required. The Cox PH model factors out the baseline hazard function from that of the covariates and assumes the hazard of an event at time (t) that is due to an exposure (X) is a function of an unknown baseline hazard, h0(t), and the

exposure (X). The equation of the hazard rate is expressed as $h(t) = h0(t)*\exp(\beta 1X+\beta 0)$ where β represents the exposure effect on the hazard of death. Under the null hypothesis, the hazard of death due to the exposure variable is equal to the baseline hazard, resulting in a hazard ratio (HR) equal to 1. In the Cox PH model, it is assumed that covariates are independent of time and hazards are proportional across the strata of a variable (risk is multiplicative) and constant over time; stratification and interaction terms that include time and the variable with non-proportional hazards can be used when the latter assumption is violated.

Results from the Kaplan-Meier survival curves, log-rank tests, and bivariate Cox PH regression models were used to inform our multivariate Cox PH models. We incorporated interaction terms between time and the independent variables of interest, such as the NCI Charlson comorbidity index score, to test for significance in the models and account for violations of the proportional hazard assumption. Tied event data (i.e., deaths occur at the same time) can pose a threat to the validity of Cox partial likelihood estimate, particularly when the number of tied events is large (coefficients are biased towards zero); to minimize the occurrence of tied events, we utilized a small interval (days) to measure time to event and the Efron approximation to account for ties that occurred. Also, although informative censoring (i.e., an existing correlation between censoring and prediction of survival such as loss of insurance coverage due to severe illness) was not expected in this Medicare-covered population, we assessed the reasons for censoring to ensure that informative censoring had not occurred.

We performed additional analyses of overall survival duration using propensity score (PS) methods to address potential treatment selection bias and assess the robustness of the original results. Observed covariates that predict treatment exposure (bevacizumab use) and are independently associated with the outcome (time to event) can confound or bias the effect measure that describes the relationship between the exposure and outcome.[217] Propensity score methods offer a useful approach to control confounding and minimize bias in effect measure estimates when the exposure of interest is dichotomous.[218] A propensity score is the conditional probability of exposure for an individual given

all measured confounders; within a group of individuals with the same propensity score, differences in the outcome between exposed and unexposed individuals is conditionally independent of the covariates.[217] Unbiased estimates of the average treatment effect can be estimated by matching on the PS between two comparable groups, by including the PS as a covariate in a multivariate model of the outcome, by stratifying on the PS, or fitting a weighted regression model using the inverse-probability of exposure weights from the estimated PS.[217, 218]

We performed two propensity score-adjusted analyses to compare the effect of bevacizumab treatment on survival among patients with similar risk profiles as assessed by measured confounders. First, we used multivariate logistic regression models to calculate propensity scores representing the probability that a patient received bevacizumab conditional on all other measured confounders in the model. In our propensity score model, we included variables that were associated with bevacizumab use and survival (true confounders) as well as variables related to survival only; our selection of covariates was based on evidence[217] that PS models that include both confounders and variables related to the outcome only provide more precise exposure effect estimates compared to those models that best predict exposure (i.e., include variables related to exposure only). In the first propensity score-adjusted analysis, discrete Cox PH regression models were fit using the propensity score as a continuous covariate in the model. In the second propensity score-adjusted analysis, exposed patients (bevacizumab) were matched to patients with the same PS from the unexposed group (chemotherapy only) in a 1:1 ratio. Discrete Cox PH regression models were then fit among the cohort of matched patients; patients for whom there was no match were excluded from this analysis.

A subgroup analysis of survival was performed for patients diagnosed with stage IV disease as the extent of the utilization and survival outcomes of bevacizumab may differ in these patients as compared to those with stage IIIB or the overall cohort in general. In addition, two separate sensitivity analyses were performed based on 1) the time interval used to identify treatment with bevacizumab and 2) the start of the follow-up period used to identify survival duration. In the first sensitivity analysis, the time period allotted to identify the use of bevacizumab from the date

chemotherapy was initiated was expanded from 8 days to 30 days. Survival duration in this analysis was measured from day of treatment initiation to the date of death or censoring, whichever occurred earlier (same as in the original analysis). In the second sensitivity analysis, to assess for potential immortal time bias, follow-up was initiated the day after completion of the treatment identification window. In the case when the 8-day treatment window was applied to identify the use of bevacizumab, follow-up time began on day 9; in the case of the 30-day treatment window, follow-up time began on day 31.

3.5.3 Aim 3

To determine whether the use of bevacizumab in combination with standard platinum-based doublet chemotherapy as first-line treatment of older adults with advanced non-small cell lung cancer is associated with an increase in hospitalizations for severe treatment-related adverse events. The *a priori* hypotheses for this study are as follows:

H6: Among older adults with advanced non-small cell lung cancer, patients who receive bevacizumab in combination with standard platinum-based doublet chemotherapy as first line treatment have a significantly greater incidence of severe adverse events (i.e., neutropenia, gastrointestinal perforation, or severe hemorrhage) resulting in hospitalization compared to patients receiving standard platinum-based doublet chemotherapy only.

3.5.3.1 Study population

This aim investigated the association between the use of bevacizumab and hospitalization for severe treatment-related adverse events among incident cases of locally advanced or metastatic (TNM stages IIIB and IV) non-small cell lung cancer in older adults. Patients with a history of cancer were excluded because prior cancer diagnoses and/or therapies may influence the use of subsequent treatments. Similarly, patients with Medicare eligibility based on end-stage renal disease or disability

were excluded as these patients are likely to be frailer and may receive different treatment or have different treatment outcomes than the general Medicare patient population. In addition, in order to accurately identify patients who were eligible to receive bevacizumab and detect relationships between bevacizumab use and the patient and health system characteristics of interest, we excluded individuals who were: diagnosed prior to reaching 66 years of age, diagnosed at death or autopsy, deceased within 30 days of diagnosis, missing any information about their diagnosis or death, diagnosed with squamous cell NSCLC (contraindication for bevacizumab), diagnosed with carcinoma in situ or stage I through stage IIIA, missing any information about their tumor stage or histology, enrolled in a Medicare Advantage Plan or had any period without Medicare Parts A and B during the 12 months before or any time following diagnosis. Furthermore, to correctly identify and describe first-line treatment received by patients within the cohort, individuals who received 'other' or unspecified chemotherapy agents or received chemotherapy in an inpatient setting (i.e., in a hospital) ≤ 8 days from the date of the first chemotherapy claim were excluded.

3.5.3.2 Dependent and key independent variables

- The dependent variables of interest in this aim included three distinct measures. The first dependent variable was a dichotomous measure of the occurrence of a hospitalization for a severe treatment-related adverse event within the first 180 days of treatment, starting follow-up time on the date of the first identified chemotherapy claim. Severe treatment-related adverse events included potentially life-threatening complications that were associated with bevacizumab during randomized clinical trials as indicated on the product safety label[207] including neutropenia, gastrointestinal perforation, and severe hemorrhage. Hospitalization for arterial thromboembolic events was included based on the increased risk associated with the use of bevacizumab found in a meta-analysis of cancer clinical trials.[206] In addition, composite measure for any of the aforementioned adverse events was also created. The

second dependent variable of interest was a dichotomous measure of the occurrence of a hospitalization for a severe treatment-related adverse event within the specified first-line treatment window. The first-line treatment window was described previously in section 3.4.1. In addition to the dichotomous measure, the third dependent variable of interest was the time to event of hospitalization for a severe treatment-related adverse event. Follow-up time was defined as the time from the date of the first identified chemotherapy claim to the first claim date of a hospitalization for an arterial thromboembolic event, neutropenia, gastrointestinal perforation, or severe hemorrhage. Patients who did not experience the specified event (hospitalization) were censored at the date of death or the end of the first-line treatment window, whichever occurred first.

- The key independent variable of interest in this aim was the use of bevacizumab within 8 days of the start of first-line treatment with standard platinum-based doublet chemotherapy.

3.5.3.3 Control variables

- Control variables considered in this aim included clinical and sociodemographic characteristics that could influence hospitalization for the specific adverse events of interest and may also have been associated with the use of bevacizumab in the first study (confounders): age, race, census tract-level information on median household income and education attainment (proxy measures of socioeconomic status), receipt of treatment from a CCOP-affiliated provider, sex, marital status at the time of diagnosis, Medicaid coverage preceding diagnosis, population density, NCI Charlson comorbidity index score, year of diagnosis, SEER region, and tumor stage, grade, and histology. In addition we also evaluated for confounding among specific comorbidities (e.g., cerebrovascular disease, chronic obstructive pulmonary disease, history of myocardial infarction, and congestive heart failure) that may have increased susceptibility to hospitalization for selected adverse events.

3.5.3.4 Methods of analysis

We conducted an evaluation of the association between bevacizumab use and any hospitalization for specific severe treatment-related adverse events using an intent-to-treat approach. Any hospitalization for arterial thromboembolic events, neutropenia, gastrointestinal perforation, or severe hemorrhage that occurred after the start of chemotherapy was attributed to the treatment regimen the patient was first initiated on. Since our primary study objective concerned the potential association between the addition of bevacizumab to first-line platinum-based doublet chemotherapy and hospitalization, our main comparison contrasted the rate of hospitalizations between patients who received bevacizumab in addition to platinum-based doublet chemotherapy with those patients who received platinum-based doublet chemotherapy only.

We first used descriptive statistics including counts and percentages to describe the cumulative incidence of hospitalizations for each of the severe adverse events within the first 180 days of treatment according to the utilization of bevacizumab. Logistic regression was then used to estimate the odds of hospitalization for each adverse event, comparing patients who received bevacizumab with those patients who did not. Bivariate analyses of each independent variable with hospitalization for each of the severe events were performed followed by multiple logistic regressions that incorporated those covariates that were significantly associated with hospitalization. Interaction terms between bevacizumab use and demographic, clinical, and site of care variables were evaluated for inclusion in the final regression models using the log likelihood ratio test (LRT); the intent of the interaction terms was to identify those covariates that modified the effect of bevacizumab on hospitalization for the specified adverse event.

For our analysis of hospitalization events during the first-line treatment window, we compared bivariate Kaplan-Meier survival curves to describe the incidence of any hospitalization for severe treatment-related adverse events by bevacizumab use. Corresponding log-rank tests were used to measure equality in the incidence of hospitalizations across strata of each independent categorical

variable and determine whether the variable should be considered for inclusion in the final prediction model. Cox proportional hazards modeling was used to estimate the independent association between bevacizumab use and hospitalization for arterial thromboembolic events, neutropenia, gastrointestinal perforation, severe hemorrhage, or the composite measure after controlling for potential confounders and independent variables associated with hospitalization. Results from the Kaplan-Meier survival curves and log-rank tests were used to inform our multivariate Cox PH models. Covariates were considered for inclusion in multivariable Cox proportional hazard models if they were significantly associated with the adverse event as indicated by a log-rank p-value of 0.05 or less. Covariates deemed to be clinically relevant were also considered for inclusion in the multivariable models. Interaction terms between time and independent variables were included in the model when the hazard rate for hospitalizations across strata of the independent variable violated the proportional hazard assumption. Tied event data (i.e., hospitalizations occur at the same time) can pose a threat to the validity of the Cox partial likelihood estimate, particularly when the number of tied events is large (coefficients are biased towards zero); to minimize the occurrence of tied events, we utilized a small interval (days) to measure time to event and the Efron approximation to account for ties that occurred. Also, although informative censoring (i.e., an existing correlation between censoring and prediction of survival such as loss of insurance coverage due to severe illness) was not expected, we assessed the reasons for censoring to ensure that informative censoring had not occurred.

Furthermore, we also evaluated the association between bevacizumab use and hospitalization for severe treatment-related adverse events using propensity score (PS) methods to address potential treatment selection bias and assess the robustness of the original results. In particular, we performed two propensity score-adjusted analyses to compare the effect of bevacizumab treatment on hospitalization for severe treatment-related adverse events among patients with similar risk profiles as assessed by measured confounders. First, we used multivariate logistic regression models to calculate propensity scores representing the probability that a patient received bevacizumab conditional on all other measured confounders in the model. In our propensity score model, we included variables that

were associated with bevacizumab use and hospitalization (true confounders) as well as variables related to hospitalization only; our selection of covariates was based on evidence[217] that PS models that include both confounders and variables related to the outcome only provide more precise exposure effect estimates compared to those models that best predict exposure (i.e., include variables related to exposure only). In the first propensity score-adjusted analysis, discrete Cox PH regression models were fit using the propensity score as a continuous covariate in the model. In the second propensity score-adjusted analysis, propensity scores were used to match exposed patients (bevacizumab) with patients from the unexposed group (chemotherapy only) in a 1:1 ratio using a 5-to-1 digit greedy-match algorithm. Discrete Cox PH regression models were then fit among the cohort of matched patients; patients for whom there was no match were excluded from this analysis.

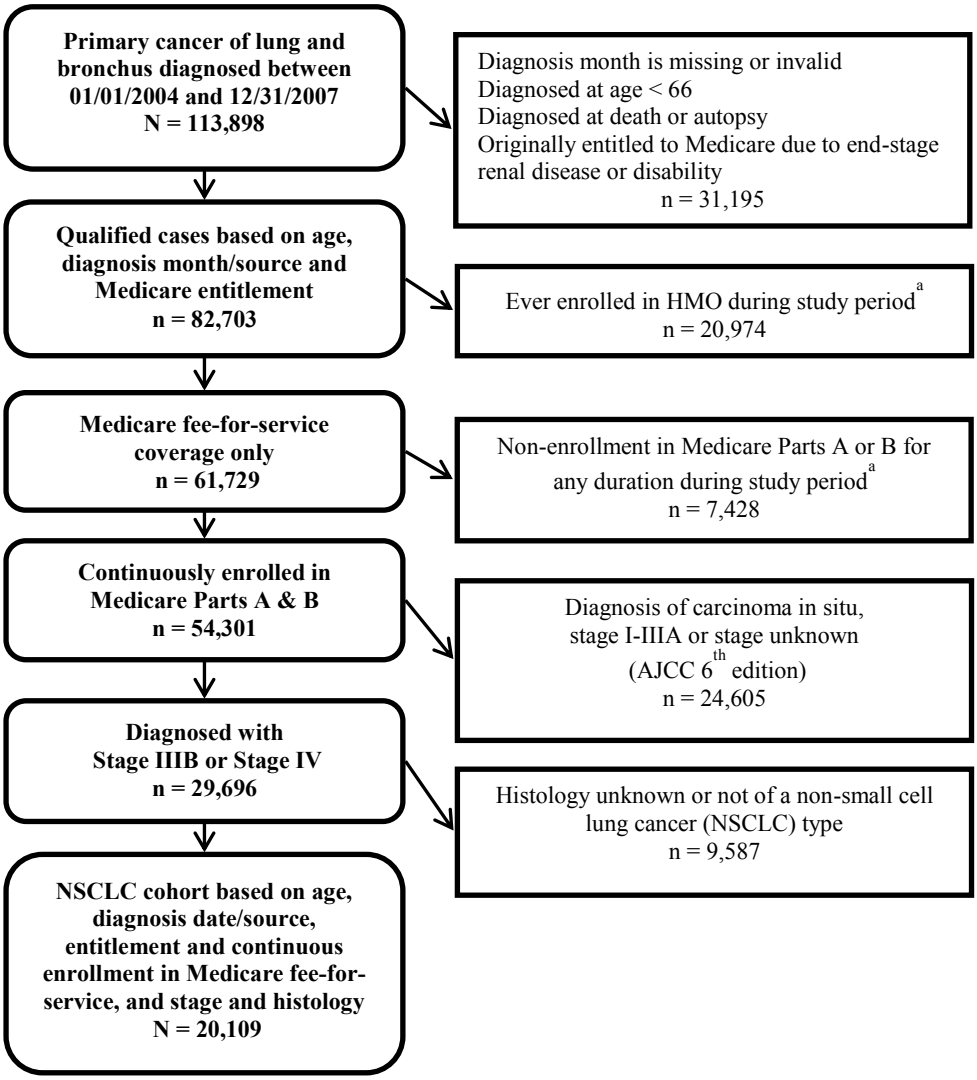
Two separate sensitivity analyses of the effect of bevacizumab on hospitalization for severe treatment-related adverse events were performed. The first sensitivity analysis assessed the effect of bevacizumab on hospitalization for severe adverse events among patients receiving carboplatin-paclitaxel as first-line treatment, a commonly selected doublet chemotherapy regimen utilized in the clinical trial that led to FDA approval of bevacizumab for the treatment of advanced NSCLC (ECOG 4599). The second sensitivity analysis assessed the effect of bevacizumab on hospitalization for severe adverse events among patients stratified by NCI Charlson comorbidity index score. Consideration for comorbidity was based on the assumption that patients with greater comorbidity may be more susceptible to hospitalization for severe treatment-related adverse events.

CHAPTER FOUR

RESULTS

4.1 Description of Sample Population

Figure 4.1: Flow diagram of NSCLC cohort selection



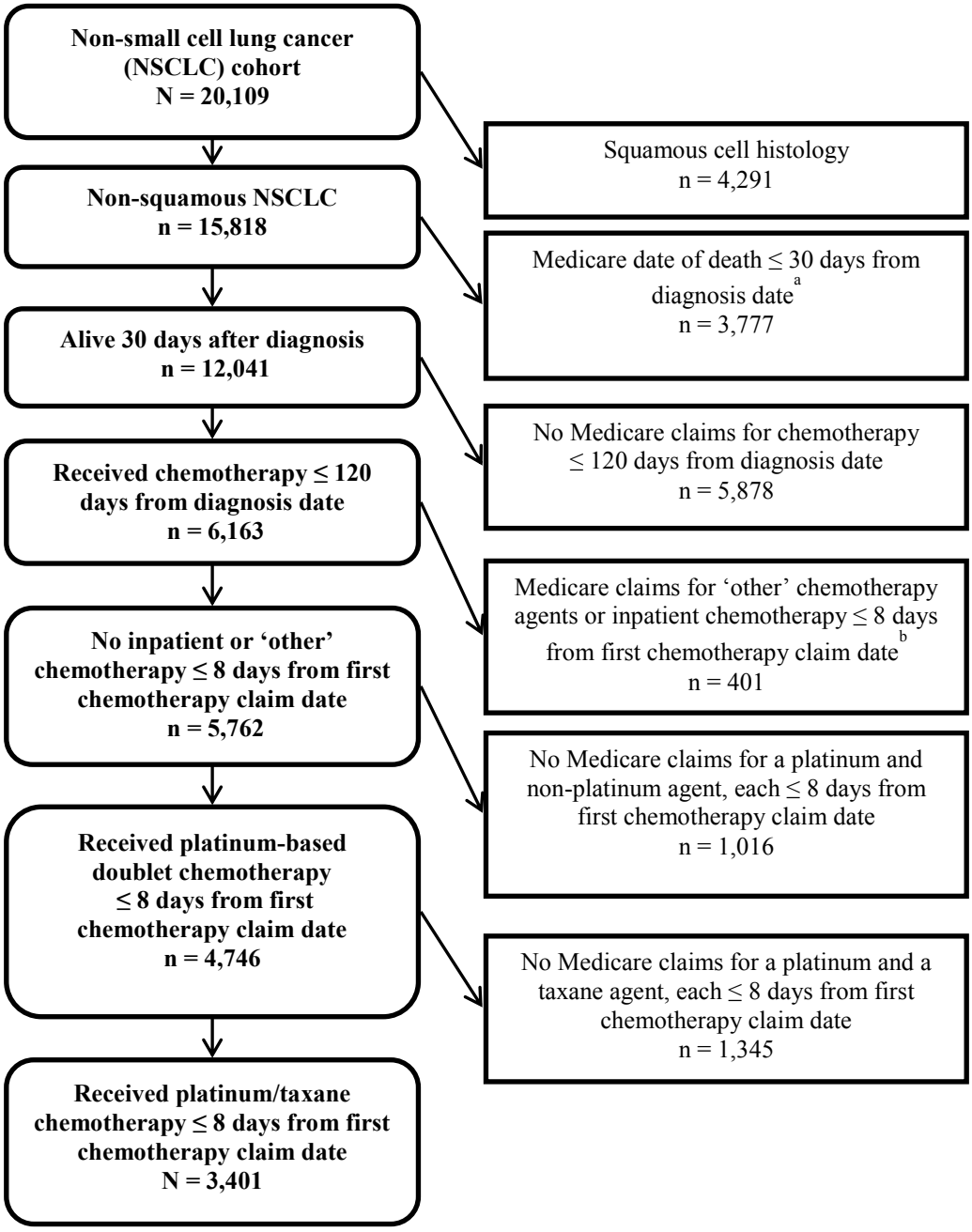
[a] Study period is from 12 months prior to diagnosis month to Medicare record of death or end of data, which ever comes earlier.

To derive a NSCLC cohort, all patients in the SEER database with a primary cancer of the lung and bronchus diagnosed between January 1, 2004 and December 31, 2007 were initially selected. Patients were included if they were diagnosed with stage IIIB or stage IV tumors and maintained enrollment in fee-for-service Medicare Parts A and B beginning 12 months prior to their month of diagnosis through their date of death or censoring, whichever came earlier. Figure 4.1 depicts the number of patients who were excluded because they: 1) had missing or invalid information about their date of diagnosis; 2) were diagnosed prior to their 66th birthday or at the time of death or autopsy; 3) were originally entitled to Medicare based on end-stage renal disease or disability; 4) were ever enrolled in a Medicare Advantage plan beginning 12 months prior to their month of diagnosis through their date of death or censoring, whichever came earlier; 5) were diagnosed with carcinoma in situ, stage I through stage IIIA, or stage unknown lung cancer; or 6) were diagnosed with a lung cancer tumor of unknown histology or not of non-small cell histology. Application of these selection criteria resulted in a cohort of 20,109 older adults with stage IIIB or stage IV NSCLC.

Additional inclusion and exclusion were then applied to the NSCLC population to obtain the final analytic cohort for this study. Patients were included if they received chemotherapy within 120 days from the date of diagnosis and received an initial treatment regimen consisting of one platinum and one non-platinum agent, each administered within the first 8 days of chemotherapy. Patients were excluded from the final cohort if they were diagnosed with a lung cancer tumor of squamous cell histology (a contraindication to the use of bevacizumab), died within 30 days from the date of diagnosis, or received 'other' unspecified chemotherapy agents or chemotherapy in an inpatient setting (i.e., in a hospital) within 8 days from the first date of chemotherapy. As illustrated in Figure 4.2, application of these additional inclusion and exclusion criteria resulted in a final analytic cohort of 4,746 older adults with stage IIIB or stage IV NSCLC who received an initial platinum-based doublet chemotherapy regimen within 120 days of diagnosis; of this group, 3,401 patients specifically

received a doublet regimen consisting of a platinum agent (carboplatin or cisplatin) and a taxane agent (paclitaxel or docetaxel).

Figure 4.2: Flow diagram of final analytic cohort selection



[a] Date of diagnosis considered the first day of the diagnosis month

[b] 'Other' chemotherapy included all chemotherapy agents not otherwise specified because of low use in NSCLC or because the agent was not identified in the Medicare claim.

Table 4.1 describes the breakdown of predisposing, enabling, and need characteristics among patients included in the final analytic cohort. The average and median ages of patients in the cohort were 73.4 years (standard deviation = 5.0) and 73.0 years, respectively. A majority of patients were diagnosed between the ages of 70 and 79 years (60.6%), male (53.0%), married (61.9%), and of white race (88.9%). In addition, most patients resided in the South (Georgia, Kentucky, Louisiana; 37.9%) and within a metropolitan area at the time of diagnosis (85.5%), but only a minority of patients received state buy-in Medicare coverage during the 12 months preceding their diagnosis (8.8%) and few received any medical or chemotherapy treatment from a CCOP-affiliated provider (36.5% and 21.6%, respectively). Evaluation of the need characteristics shows that a majority of patients were diagnosed with stage IV cancer (70.9%), as well as tumors of unknown grade (59.5%), and adenocarcinoma histology (55.7%). Furthermore, most patients receiving chemotherapy treatment with a platinum-based doublet regimen had a low level of comorbidity, as indicated by the percentage with an NCI Charlson Comorbidity Index of zero (59.3%) or one (33.3%). Hemoptysis and brain metastases were present in 4.1% and 23.6% of patients at the time of diagnosis, respectively, while 6.4% of patients had a form of cancer-directed surgery.

Table 4.1 Predisposing, enabling, and need characteristics of the cohort (N = 4746)

Predisposing	n (%)	Enabling	n (%)	Need	n (%)
Age at diagnosis		Median household income (census tract level)		Tumor stage	
66 to 69	1260 (26.5)	Lowest quartile	976 (20.6)	IIIB	1380 (29.1)
70 to 79	2878 (60.6)	Second	1179 (24.8)	IV	3366 (70.9)
80 and older	608 (12.8)	Third	1224 (25.8)		
		Highest	1363 (28.7)		
Sex		Population density		Summary stage	
Female	2232 (47.0)	Urban/rural	689 (14.5)	Regional	410 (8.6)
Male	2514 (53.0)	Metro	4057 (85.5)	Distant	4336 (91.4)
Marital status		State buy-in Medicare coverage during year preceding diagnosis		Grade	
Not married	1809 (38.1)	No	4330 (91.2)	Well/Moderately differentiated	543 (11.4)
Married	2937 (61.9)	Yes	416 (8.8)	Poor/Undifferentiated	1382 (29.1)
				Unknown	2821 (59.4)
Race		≥ 50% of medical claims from CCOP provider		Tumor histology	
White	4219 (88.9)	No	2830 (59.6)	Adenocarcinoma	2642 (55.7)
Black	288 (6.1)	Yes	1736 (36.5)	Large cell	256 (5.4)
Other	239 (5.0)			Other and NOS	1848 (38.9)
% 25 years and older in census tract w/ < HS education		≥ 50% of chemotherapy claims from CCOP provider		NCI Charlson Comorbidity Index	
Lowest quartile	1339 (28.2)	No	3541 (74.6)	0	2814 (59.3)
Second	1241 (26.1)	Yes	1025 (21.6)	1	1580 (33.3)
Third	1198 (25.2)			2	235 (5.0)
Highest	959 (20.2)				
		Received treatment from provider affiliated with a: Cooperative research group		Hemoptysis	
		No	1965 (41.4)	No	4550 (95.9)
		Yes	2445 (51.5)	Yes	196 (4.1)
		NCI designated cancer center		Brain metastases	
		No	4128 (87.0)	No	3625 (76.4)
		Yes	282 (5.9)	Yes	1121 (23.6)

Table 4.1 (Continued)

Predisposing	n (%)	Enabling	n (%)	Need	n (%)
		Teaching hospital		Radiation therapy received	
		No	1962 (41.3)	No	2366 (49.9)
		Yes	2442 (51.5)	Yes	2314 (48.8)
		Medical school		Cancer-directed surgery	
		No	2171 (45.7)	No	4441 (93.6)
		Yes	2239 (47.2)	Yes	305 (6.4)
		Year of diagnosis			
		2004-2005	2378 (50.1)		
		2006	1242 (26.2)		
		2007	1126 (23.7)		
		SEER region[a]			
		East	1107 (23.3)		
		Midwest	893 (18.8)		
		South	1796 (37.9)		
		West	950 (20.0)		

[a] SEER regions: East = Connecticut and New Jersey ; Midwest = Iowa, Michigan, New Mexico, and Utah; South = Georgia, Kentucky, and Louisiana; West = California, Hawaii, and Washington

Abbreviations: CCOP = Community Clinical Oncology Program; NCI = National Cancer Institute; SEER = Surveillance Epidemiology and End Results.

4.2 Description of Chemotherapy Use

Table 4.2 provides descriptive statistics about the platinum-based chemotherapy received by patients within the cohort, including the specific chemotherapy agent combinations used and their median duration of use. Among the platinum agents available for use, carboplatin (92.4%) was utilized more frequently than either cisplatin (7.5%) or oxaliplatin (0.1%) during first-line treatment. Paclitaxel was the chemotherapeutic agent most often used in combination with a platinum compound (2699/4746, 56.9%) while docetaxel (702/4746, 14.8%) and gemcitabine (947/4746, 20.0%) were also utilized among a considerable proportion of patients. Overall, the majority of patients received a platinum and taxane doublet regimen (71.7%), with most receiving a combination of carboplatin and paclitaxel (56.5%) specifically.

The median duration of treatment, measured as the median number of days between the first claim date of chemotherapy and the last claim date of one of the two chemotherapy agents (whichever agent was stopped first), varied by regimen. Among the platinum and taxane regimens, chemotherapy combinations involving carboplatin had a median duration of 63 days and an interquartile range (IQR) of approximately 25 to 111 days; by comparison, cisplatin and taxane regimens had shorter median durations of use at 42 days (IQR, 20 to 121 days). Median duration of treatment among the more commonly used non-taxane regimens ranged from 32 days with cisplatin and etoposide (IQR, 25 to 56 days) to 70 days with carboplatin and etoposide (IQR, 30 to 107 days) as well as with cisplatin and gemcitabine (IQR, 22 to 119 days).

Table 4.2 First-line platinum-based doublet chemotherapy regimens used

Chemotherapy regimen	N	%	Regimen duration (days)[a] Median	IQR (25% - 75%)
Platinum and taxane doublet	**3401**	**71.66**	**63**	**28 – 106**
Carboplatin with				
Paclitaxel	2683	56.53	63	28 – 106
Docetaxel	637	13.42	63	25 – 111
Cisplatin with				
Paclitaxel	16	0.34	42	20 – 121
Docetaxel	65	1.37	42	21 – 70
Platinum and non-taxane doublet	**1345**	**28.34**	**55**	**23 – 105**
Carboplatin with				
Gemcitabine	888	18.71	62	21 – 106
Etoposide	129	2.72	70	30 – 107
Pemetrexed	30	0.63	73	26 – 105
Vinorelbine	18	0.38	66	28 – 105
Irinotecan	2	0.04	116	86 – 147
Cyclophosphamide	1	0.02	--[b]	--
Cisplatin with				
Etoposide	175	3.69	32	25 – 56
Gemcitabine	59	1.24	70	22 – 119
Vinorelbine	29	0.61	44	28 – 98
Irinotecan	7	0.15	35	1 – 156
Pemetrexed	2	0.04	94	63 – 126
Oxaliplatin with				
5-Fluorouracil	3	0.06	28	14 – 92
Gemcitabine	2	0.04	10	1 – 21

[a] Regimen duration defined as the number of days between the first and last Medicare claim dates for the chemotherapy regimen; when the first and last claim dates for each of the two chemotherapy agents were not identical, the first and last Medicare claim dates were considered the earliest of the initial and earliest of the final claim dates between the two chemotherapy agents, respectively.
[b] Patient only received one administration of the combination of carboplatin and cyclophosphamide
Abbreviations: IQR = Interquartile range

4.3 Aim 1: Utilization of Bevacizumab

The intent of the Aim 1 was to describe the utilization of bevacizumab in combination with standard platinum-based doublet chemotherapy as first line treatment of older adults with advanced NSCLC and to identify the clinical, sociodemographic, and health system factors associated with its use. The clinical, demographic, and health system factors were categorized based on Andersen's Behavioral Model of Health Services Use to assess whether predisposing, enabling, or need characteristics were more closely linked to the use of bevacizumab.

The utilization of bevacizumab within 8 days of the start of platinum-based doublet chemotherapy is described according to specific treatment regimen in Table 4.3. Overall, 386 of the 4,746 (8.1%) patients in the cohort received bevacizumab. Bevacizumab was utilized more often among patients receiving a platinum and taxane doublet (9.8%) than among patients receiving a platinum and non-taxane doublet treatment (3.9%). Although bevacizumab was used in combination with ten different chemotherapy regimens, over 95% of patients who received bevacizumab had it administered alongside one of three carboplatin-based treatments in particular: carboplatin and paclitaxel (266/386, 68.5%), carboplatin and docetaxel (66/386, 16.9%), or carboplatin and gemcitabine (38/386, 9.8%). Compared to just 2.5% of patients receiving a cisplatin-based doublet regimen, approximately 9% of patients who received a carboplatin-based doublet also received bevacizumab.

The median duration of bevacizumab use, measured as the median number of days between the first and last claim dates for bevacizumab, varied by chemotherapy regimen. Among patients who received bevacizumab in addition to a platinum and taxane doublet regimen, the median duration of bevacizumab treatment was 76 days (IQR, 29 to 112 days). The median duration of bevacizumab treatment was 64 days (IQR, 21 to 137 days) among patients who received bevacizumab in addition to a platinum and non-taxane doublet regimen. Among the specific regimens most commonly used with bevacizumab, the median duration of bevacizumab use was similar among patients who received

either carboplatin and paclitaxel (median, 105 days; IQR, 42 to 217 days) or carboplatin and docetaxel (median, 101 days; IQR, 42 to 219 days) and greater than that seen among patients who received carboplatin and gemcitabine (median, 64 days; IQR, 21 to 132 days).

Table 4.3 Use of bevacizumab within 8 days of chemotherapy start

				Duration of bevacizumab use[a]	
Chemotherapy regimen	**Total receiving chemotherapy**	**No. receiving bevacizumab**	**%**	**Median (days)**	**IQR (25% - 75%)**
Platinum and taxane	**3401**	**333**	**9.8**	**76**	**29 - 112**
Carboplatin with					
Paclitaxel	2683	266	9.9	105	42 – 217
Docetaxel	637	66	10.4	101	42 – 219
Cisplatin with					
Paclitaxel	16	0	0.0	--	--
Docetaxel	65	1	1.5	208	61 – 356
Platinum and non-taxane	**1345**	**53**	**3.9**	**64**	**21 - 137**
Carboplatin					
Gemcitabine	888	38	4.3	64	21 – 132
Etoposide	129	1	0.8	--[b]	--
Pemetrexed	30	7	23.3	42	23 – 112
Vinorelbine	18	0	0.0	--	--
Irinotecan	2	0	0.0	--	--
Cyclophosphamide	1	0	0.0	--	--
Cisplatin					
Etoposide	175	1	0.6	105	--
Gemcitabine	59	5	8.5	201	154 – 252
Vinorelbine	29	0	0.0	--	--
Irinotecan	7	0	0.0	--	--
Pemetrexed	2	0	0.0	--	--
Oxaliplatin					
5-fluorouracil	3	1	33.3	14	--
Gemcitabine	2	0	0.0	--	--

[a]Duration of use defined as the number of days between the first and last Medicare claim dates for bevacizumab

[b] Patient only received one administration of bevacizumab

4.3.1 Bivariate analysis of the use of bevacizumab

The following subsections describe the potential bivariate associations between predisposing, enabling, and need variables of interest and the utilization of bevacizumab with platinum-based doublet chemotherapy. The associations between each set of characteristics and the use of bevacizumab among patients who received platinum-taxane doublet chemotherapy regimens in particular are described separately from the larger cohort analysis.

4.3.1.1 Any platinum-based doublet chemotherapy

The bivariate analysis results comparing the characteristics of patients who received platinum-based chemotherapy with bevacizumab to those patients who received chemotherapy only are presented in Table 4.4.

Age, race, socioeconomic status, and provider CCOP-affiliation

Estimated odds ratios (OR) suggested that patients aged 70 to 79 and 80 and older had decreased odds of receiving bevacizumab compared to patients aged 66 to 69. Among racial groups, blacks had the lowest odds of receiving bevacizumab whereas patients of non-white/non-black race had the highest. Patients in census tracts within the lowest quartile for percentage of adults with less than a high school education (i.e., census tracts with higher educational attainment) or in the highest quartile of median household income also had the highest odds of bevacizumab use. However, age, race, and socioeconomic status measures were not significantly ($p<0.05$) associated with the use of bevacizumab among patients receiving any platinum-based chemotherapy regimen. Conversely, patients who received at least 50% of their chemotherapy from a CCOP-affiliated provider had over 50% greater odds of receiving bevacizumab as compared to patients who did not (OR 1.51, 95% CI 1.20-1.91).

Additional predisposing variables

Married patients had a 22% higher odds of receiving bevacizumab compared to noon-married patients and females had a slight greater odds of receiving bevacizumab compared to males, but neither of these predisposing variables were significantly associated ($p<0.05$) with the use of bevacizumab among patients receiving any platinum-based chemotherapy regimen.

Additional enabling variables

Year of diagnosis was significantly associated with the use of bevacizumab. Compared to patients diagnosed between 2004 and 2005, patients diagnosed in 2006 (OR 7.65; 95% CI 5.37-10.89) or 2007 (OR 12.16, 95% CI 8.61-17.16) were considerably more likely to receive bevacizumab; patients diagnosed in 2007 were also more likely to receive bevacizumab compared to patients diagnosed in 2006 (OR 1.59, 95% CI 1.26-2.00). However, additional enabling variables including population density (i.e., residence in a rural or urban residential area versus a major metropolitan area), state buy-in of Medicare coverage during the year preceding diagnosis, SEER region, and receipt of treatment from a provider affiliated with a cooperative research group, an NCI designated cancer center, teaching hospital, or medical school were not significantly associated with the use of bevacizumab among patients receiving any platinum-based doublet regimen.

Need variables

Unlike the predisposing and enabling characteristics, nearly all of the need characteristics, including tumor stage, summary stage, tumor histology, NCI Charlson comorbidity index score, hemoptysis, brain metastases, receipt of radiation therapy, and receipt of cancer-directed surgery were significantly associated with the use of bevacizumab among patients who received any platinum-based doublet chemotherapy regimen. Tumor grade was the lone need characteristic not significantly associated with the use of bevacizumab.

Table 4.4 Bivariate associations with the use of bevacizumab among patients who received platinum-based doublet chemotherapy

Characteristic	Platinum-based doublet chemotherapy: With Bevacizumab (n = 386)	Platinum-based doublet chemotherapy: Without Bevacizumab (n = 4360)	Unadjusted OR	95% CI	p-value
Predisposing					
Age at diagnosis					0.383
66 to 69	112	1148	ref		
70 to 79	231	2647	0.89	(0.71, 1.13)	
80 and older	43	565	0.78	(0.54, 1.12)	
Sex					0.635
Female	186	2046	ref		
Male	200	2314	0.95	(0.77, 1.17)	
Marital Status					0.078
Not married	131	1678	ref		
Married	255	2682	1.22	(0.98, 1.52)	
Race					0.418
White	346	3873	ref		
Black	18	270	0.75	(0.46, 1.22)	
Other	22	217	1.13	(0.72, 1.78)	
% 25 years and older in census tract w/ < HS education					0.543
Lowest quartile	121	1218	ref		
Second	97	1144	0.82	(0.60, 1.11)	
Third	96	1102	0.85	(0.65, 1.13)	
Highest	72	887	0.88	(0.66, 1.16)	

Table 4.4 (Continued)

Enabling					

Median household income (census tract level)					0.754
Lowest quartile	82	895	ref		
Second	94	1087	0.93	(0.69, 1.29)	
Third	94	1130	0.92	(0.67, 1.25)	
Highest	121	1244	1.06	(0.79, 1.42)	
Population density					0.759
Urban/rural	54	635	ref		
Metro	332	3725	1.05	(0.78, 1.41)	
State buy-in Medicare coverage during year preceding diagnosis					0.595
No	355	3975	ref		
Yes	31	385	0.90	(0.62, 1.32)	
≥ 50% of medical claims from CCOP provider					0.037
No	213	2617	ref		
Yes	161	1575	1.26	(1.01, 1.56)	
≥ 50% of chemotherapy claims from CCOP provider					<0.001
No	263	3278	ref		
Yes	111	914	1.51	(1.20, 1.91)	
Received treatment from provider affiliated with a:					
Cooperative research group					0.819
No	161	1804	ref		
Yes	205	2240	1.02	(0.83, 1.27)	
NCI cancer center					0.929
No	343	3785	ref		
Yes	23	259	0.98	(0.63, 1.52)	

Table 4.4 (Continued)

Teaching hospital					0.927
No	163	1799	ref		
Yes	201	2241	0.99	(0.80, 1.23)	
Medical school					0.758

No	183	1988	ref		
Yes	183	2056	0.97	(0.78, 1.20)	
Year of diagnosis					<0.001
2004-2005	41	2337	ref		
2006	147	1095	7.65	(5.37, 10.89)	
2007	198	928	12.16	(8.61, 17.16)	
SEER region					0.103
East	71	1036	ref		
Midwest	73	820	1.30	(0.92, 1.82)	
South	161	1635	1.44	(1.07, 1.92)	
West	81	869	1.36	(0.98, 1.89)	
Need					
Tumor stage					<0.001
IIIB	74	1306	ref		
IV	312	3054	1.80	(1.39, 2.34)	
Summary stage					<0.001
Regional	15	395	ref		
Distant	371	3965	2.46	(1.45, 4.17)	
Grade					0.187
Well/Moderately differentiated	49	494	ref		
Poor/Undifferentiated	100	1282	0.79	(0.55, 1.12)	
Unknown	237	2584	0.92	(0.67, 1.28)	

Table 4.4 (Continued)

Tumor histology					<0.001
Adenocarcinoma	261	2381	Ref		
Large cell	12	244	0.45	(0.25, 0.81)	
Other and NOS	113	1735	0.59	(0.47, 0.75)	
NCI Comorbidity Index					0.014
0	248	2566	Ref		

1	116	1464	0.82	(0.65, 1.03)	
2	9	226	0.41	(0.21, 0.81)	
Hemoptysis					0.038
No	378	4172	Ref		
Yes	8	188	0.47	(0.23, 0.96)	
Brain metastases					<0.001
No	323	3302	Ref		
Yes	63	1058	0.61	(0.46, 0.80)	
Radiation therapy received					<0.001
No	263	2103	Ref		
Yes	113	2201	0.41	(0.33, 0.52)	
Cancer-directed surgery					0.021
No	369	4035	ref		
Yes	15	306	0.54	(0.32, 0.91)	

[a] SEER regions: East = Connecticut and New Jersey ; Midwest = Iowa, Michigan, New Mexico, and Utah; South = Georgia, Kentucky, and Louisiana; West = California, Hawaii, and Washington

Abbreviations: OR = Odds ratio; CI = Confidence interval; NCI = National Cancer Institute; NOS = Not otherwise specified; SEER = Surveillance Epidemiology and End Results.

Patients with stage IV tumors at diagnosis were 80% more likely to receive bevacizumab in addition to platinum-based doublet chemotherapy as patients diagnosed with stage IIIB tumors (OR 1.80, 95% CI 1.39-2.34). Similarly, patients with distant stage disease at diagnosis were approximately 2.5 times as likely to have bevacizumab added to their platinum-based doublet regimen as patients diagnosed with regional tumors (OR 2.46, 95% CI 1.45-4.17). Compared to patients with adenocarcinoma histology, patients with large cell (OR 0.45, 95% CI 0.25-0.81) or histology unknown or not otherwise specified (OR 0.59, 95% CI 0.47-0.75) were significantly less likely to receive bevacizumab. Furthermore, as the comorbidity burden of patients increased, the use of bevacizumab decreased; patients with an NCI Charlson comorbidity index score of 2 were less than half as likely to receive bevacizumab compared to patients with a score of 0 (OR 0.41, 95% CI 0.21-0.81). Likewise, patients with hemoptysis (OR 0.47, 95% CI 0.23-0.96) or brain metastases (OR 0.61, 95% CI 0.46-0.80) had a significantly decreased likelihood of receiving bevacizumab in contrast to patients without these complications at the time of diagnosis. Lastly, patients who were treated with radiation (OR 0.41, 95% CI 0.33-0.52) or cancer-directed surgery (OR 0.54, 95% CI 0.32-0.91) were about half as likely to receive bevacizumab as patients who were not.

4.3.1.2 Platinum-taxane doublet chemotherapy only

The bivariate analysis results comparing the characteristics of patients who received platinum-taxane doublet chemotherapy with bevacizumab to those patients who received platinum-taxane chemotherapy only are described in Table 4.5.

Age, race, socioeconomic status, and provider CCOP-affiliation

Similar to the results among patients receiving any platinum-based doublet chemotherapy, estimated ORs suggested that utilization of bevacizumab among patients who received a platinum-taxane regimen was lower among those aged 70 to 79 and 80 and older compared to patients aged 66

to 69. In addition, blacks had the lowest odds of receiving bevacizumab among racial groups whereas patients of non-white/non-black race had the highest. Patients in census tracts with higher education attainment (i.e., lowest quartile of education measure) or higher median household income also had the highest odds of bevacizumab use. However, age, race, and socioeconomic status measures were not significantly ($p<0.05$) associated with the use of bevacizumab among patients receiving platinum-taxane chemotherapy. Still, patients who received at least half of their chemotherapy treatment from a CCOP-affiliated provider had 50% greater odds of receiving bevacizumab compared to patients who did not (OR 1.50, 95% CI 1.17-1.93).

Additional predisposing variables

Although married patients had 20% greater odds of receiving bevacizumab compared to non-married patients (OR 1.20, 95% CI 0.95, 1.53), there were no significant associations between additional predisposing characteristics (sex and marital status) and the use of bevacizumab.

Additional enabling variables

In general, the results among patients receiving platinum-taxane chemotherapy were similar to the results seen among patients receiving any platinum-based chemotherapy regimen as year of diagnosis was the only additional enabling variable significantly associated with the use of bevacizumab. Estimates comparing the use of bevacizumab across regions of SEER registries were not statistically significant, but patients in both the West (California, Hawaii, and Washington registries) and South (Georgia, Kentucky, and Louisiana) regions were approximately 50% more likely to receive bevacizumab compared to patients in the East (Connecticut and New Jersey registries) region.

Table 4.5 Bivariate associations with the use of bevacizumab among patients who received platinum-taxane doublet chemotherapy

Characteristic	Platinum-taxane doublet chemotherapy: With Bevacizumab (n = 336)	Platinum-taxane doublet chemotherapy: Without Bevacizumab (n = 3068)	Unadjusted OR	95% CI	p-value
Predisposing					
Age at diagnosis					0.298
66 to 69	93	793	ref		
70 to 79	205	1864	0.94	(0.72, 1.21)	
80 and older	35	411	0.73	(0.48, 1.09)	
Sex					0.868
Female	158	1441	ref		
Male	175	1627	0.98	(0.78, 1.23)	
Marital Status					0.126
Not married	114	1182	ref		
Married	219	1886	1.20	(0.95, 1.53)	
Race					0.316
White	294	2746	ref		
Black	18	184	0.91	(0.55, 1.50)	
Other	21	138	1.42	(0.88, 2.28)	
% 25 years and older in census tract w/ < HS education					0.128
Lowest quartile	108	807	ref		
Second	82	809	0.76	(0.55, 1.02)	
Third	81	805	0.75	(0.55, 1.02)	
Highest	62	641	0.72	(0.53, 1.00)	

Table 4.5 (Continued)

Enabling					

Median household income (census tract level)					0.350
Lowest quartile	68	669	ref		
Second	80	769	1.02	(0.73, 1.44)	
Third	80	803	0.98	(0.70, 1.38)	
Highest	105	825	1.25	(0.91, 1.73)	
Population density					0.364
Urban/rural	46	482	ref		
Metro	287	2586	1.16	(0.84, 1.61)	
State buy-in Medicare coverage during year preceding diagnosis					0.766
No	307	2814	ref		
Yes	26	254	0.94	(0.62, 1.43)	
≥ 50% of medical claims from CCOP provider					0.229
No	183	1763	ref		
Yes	142	1187	1.15	(0.92, 1.45)	
≥ 50% of chemotherapy claims from CCOP provider					0.001
No	224	2269	ref		
Yes	101	681	1.50	(1.17, 1.93)	
Received treatment from provider affiliated with a:					
Cooperative research group					0.977
No	176	1566	ref		
Yes	143	1268	1.00	(0.79, 1.26)	
NCI cancer center					0.591
No	303	2671	ref		
Yes	16	163	0.86	(0.51, 1.47)	

Table 4.5 (Continued)

Teaching hospital					0.880
No	147	1325	ref		
Yes	170	1505	1.02	(0.81, 1.29)	

Medical school					0.868
No	165	1452	ref		
Yes	154	1382	0.98	(0.78, 1.24)	
Year of diagnosis					<0.001
2004-2005	34	1659	ref		
2006	132	782	8.23	(5.60, 12.12)	
2007	167	627	12.99	(8.89, 19.00)	
SEER region					0.064
East	61	762	ref		
Midwest	62	561	1.38	(0.95, 2.00)	
South	141	1181	1.49	(1.09, 2.04)	
West	69	564	1.53	(1.06, 2.19)	
Need					
Tumor stage					<0.001
IIIB	63	957	ref		
IV	270	2111	1.94	(1.46, 2.58)	
Summary stage					<0.001
Regional	12	306	ref		
Distant	321	2762	2.96	(1.65, 5.34)	
Grade					0.228
Well/Moderately differentiated	38	368	ref		
Poor/Undifferentiated	85	900	0.91	(0.61, 1.37)	
Unknown	210	1800	1.13	(0.79, 1.62)	

Table 4.5 (Continued)

Tumor histology					<0.001
Adenocarcinoma	223	1707	ref		
Large cell	9	171	0.40	(0.20, 0.80)	
Other and NOS	101	1190	0.65	(0.51, 0.83)	

NCI Comorbidity Index					0.005
0	219	1811	ref		
1	99	1019	0.80	(0.62, 1.03)	
2	6	167	0.30	(0.13, 0.68)	
Hemoptysis					0.078
No	325	2930	ref		
Yes	8	138	0.52	(0.25, 1.08)	
Brain metastases					0.002
No	276	2304	ref		
Yes	57	764	0.62	(0.46, 0.84)	
Radiation therapy received					<0.001
No	224	1379	ref		
Yes	99	1648	0.37	(0.29, 0.47)	
Cancer-directed surgery					0.012
No	320	2837	ref		
Yes	11	214	0.46	(0.25, 0.84)	

[a] SEER regions: East = Connecticut and New Jersey ; Midwest = Iowa, Michigan, New Mexico, and Utah; South = Georgia, Kentucky, and Louisiana; West = California, Hawaii, and Washington

Abbreviations: OR = Odds ratio; CI = Confidence interval; NCI = National Cancer Institute; NOS = Not otherwise specified; SEER = Surveillance Epidemiology and End Results.

Need variables

In general, the results among patients receiving platinum-taxane chemotherapy were similar to the results seen among patients receiving any platinum-based chemotherapy regimen. For instance, tumor stage, summary stage, tumor histology, NCI Charlson comorbidity index score, brain metastases, receipt of radiation therapy, and receipt of cancer-directed surgery all were significantly associated with the use of bevacizumab among patients receiving platinum-taxane chemotherapy. In these results, patients diagnosed with distant stage disease were nearly 3 times as likely to receive bevacizumab compared to patients diagnosed with regional stage tumors (OD 2.96, 95% CI 1.65-5.34). Patients in worse overall health with an NCI Charlson comorbidity index score of 2 were approximately 70% less likely to receive bevacizumab in contrast to healthier patients with an NCI Charlson comorbidity index score of 0 (OR 0.30, 95% CI 0.13-0.68). Tumor grade was not significantly associated with the use of bevacizumab ($p = 0.228$) and though the OR estimate suggested patients with hemoptysis were about 48% less likely to receive bevacizumab compared to patients without, the association was not statistically significant ($p = 0.078$).

4.3.2 Multivariate analysis of the use of bevacizumab

The following subsections describe the multivariate analysis of the associations between the predisposing, enabling, and need characteristics of interest and the utilization of bevacizumab among patients receiving platinum-based doublet chemotherapy. Multivariate analysis of the associations between predisposing, enabling, and need characteristics and the use of bevacizumab among patients specifically receiving platinum-taxane chemotherapy regimens are described separately.

4.3.2.1 Any platinum-based doublet chemotherapy

The multivariate analysis of the associations between predisposing, enabling, and need characteristics and the use of bevacizumab among patients receiving any platinum-based doublet chemotherapy are presented in Table 4.6.

As in the bivariate analysis, age, race, and socioeconomic status measures were unrelated to the use of bevacizumab, but receipt of treatment from a CCOP affiliated provider remained a significant independent predictor of bevacizumab use. For example, patients who received ≥ 50% of their chemotherapy from a CCOP-affiliated provider maintained 61% greater odds of receiving bevacizumab than patients who did not after controlling for other predisposing, enabling, and need characteristics (OR 1.64, 95% CI 1.25-2.16). Additional predisposing characteristics sex and marital status remained unrelated to the use of bevacizumab, whereas year of diagnosis was the only additional enabling characteristic significantly linked to the use of bevacizumab. Of the need characteristics included in the multivariate logistic regression model, tumor stage, histology, NCI Charlson comorbidity index, brain metastases at diagnosis, receipt of radiation, and receipt of cancer-directed surgery were all associated with the use of bevacizumab. Though patients with hemoptysis had approximately 50% less odds of receiving bevacizumab than patients without, this result was not statistically significant (OR 0.50, 95% CI 0.24-1.07). Similarly, tumor summary stage was no longer significantly associated with bevacizumab use after other predisposing, enabling, and need characteristics were controlled for in the regression model (OR 1.27, 95% CI 0.66-2.44).

Table 4.6 Multivariate associations of predisposing, enabling, and need characteristics on the odds of bevacizumab use among patients receiving platinum-based doublet chemotherapy

Characteristic	Adjusted OR	95% CI	p-value
Predisposing			
Age			0.174
66 to 69	Ref		
70 to 79	0.86	(0.66, 1.13)	
80 and older	0.68	(0.45, 1.02)	
Sex			0.611
Female	Ref		
Male	0.94	(0.74, 1.20)	
Marital status			0.181
Not married	Ref		
Married	1.19	(0.92, 1.55)	
Race			0.507
White	Ref		
Black	0.73	(0.42, 1.26)	
Other	1.05	(0.60, 1.83)	
% 25 years and older in census tract w/ < HS education			0.770
Lowest quartile	Ref		
Second	0.88	(0.63, 1.23)	
Third	0.82	(0.55, 1.21)	
Highest	0.81	(0.49, 1.32)	
Enabling			
Median household income (census tract level)			0.669
Lowest quartile	Ref		
Second	0.80	(0.53, 1.20)	
Third	0.76	(0.47, 1.21)	
Highest	0.81	(0.48, 1.37)	
Population density			0.248
Urban/Rural	Ref		
Metro	1.26	(0.85, 1.85)	
State buy-in Medicare coverage during year preceding diagnosis			0.722
No	Ref		
Yes	0.92	(0.58, 1.46)	
≥ 50% of chemotherapy claims from CCOP provider			<0.001
No	Ref		
Yes	1.64	(1.25, 2.16)	
Year of diagnosis			<0.001
2004-2005	Ref		
2006	8.29	(5.72, 12.03)	
2007	12.96	(8.99, 18.66)	

Table 4.6 (Continued)

SEER region			0.196
East	ref		
Midwest	1.22	(0.81, 1.83)	
South	1.43	(1.02, 2.16)	
West	1.37	(0.93, 2.01)	
Need			
Tumor stage			0.002
IIIB	ref		
IV	1.66	(1.20, 2.29)	
Summary stage			0.470
Regional	ref		
Distant	1.27	(0.66, 2.44)	
Grade			0.929
Well/Moderately differentiated	ref		
Poor/Undifferentiated	0.93	(0.61, 1.41)	
Unknown	0.98	(0.67, 1.42)	
Histology			0.001
Adenocarcinoma	ref		
Large cell	0.54	(0.28, 1.05)	
Other and NOS	0.64	(0.49, 0.83)	
NCI Charlson Comorbidity Index			0.018
0	ref		
1	0.79	(0.61, 1.02)	
2	0.42	(0.21, 0.85)	
Hemoptysis			0.073
No	ref		
Yes	0.50	(0.24, 1.07)	
Brain metastases			0.008
No	ref		
Yes	0.65	(0.47, 0.89)	
Radiation therapy received			<0.001
No	ref		
Yes	0.41	(0.32, 0.54)	
Cancer-directed surgery			0.018
No	ref		
Yes	0.47	(0.25, 0.88)	

Abbreviations: OR = Odds ratio; CI = Confidence interval; CCOP = Clinical Community Oncology Program; NOS = Not otherwise specified; NCI = National Cancer Institute

4.3.2.2 Platinum-taxane doublet chemotherapy only

The multivariate analysis of the associations between predisposing, enabling, and need characteristics and the use of bevacizumab among patients receiving platinum-taxane doublet chemotherapy are presented in Table 4.7.

Similar to the multivariate analysis of patients receiving any platinum-based doublet regimen, age, race, and socioeconomic status measures were not associated with the use of bevacizumab whereas provider CCOP-affiliation was. For instance, patients receiving ≥ 50% of chemotherapy from a CCOP-affiliated provider maintained 60% greater odds of receiving bevacizumab compared to patients who did not (OR 1.60, 95%CI 1.19-2.15). Additional predisposing characteristics were unrelated to the use of bevacizumab whereas patients diagnosed in 2006 or 2007 were significantly more likely to use bevacizumab compared to patients diagnosed in either 2004 or 2005. Patients diagnosed with stage IV tumors also had approximately 70% greater odds of bevacizumab use compared to patients with stage IIIB tumors after controlling for other characteristics. Furthermore, tumor histology, NCI Charlson comorbidity index, brain metastases, receipt of radiation therapy, and cancer-directed surgery were all significantly associated with the use of bevacizumab among patients receiving platinum-taxane chemotherapy regimens; specifically, patients with adenocarcinoma histology, NCI Charlson comorbidity index scores of zero, no brain metastases at diagnosis, no radiation treatment, and no cancer-directed surgery had greater odds of receiving bevacizumab. Despite significant bivariate associations, summary stage, tumor grade, hemoptysis, and cancer-directed surgery were not significantly linked to the use of bevacizumab after controlling for other predisposing, enabling, and need characteristics.

Table 4.7 Multivariate associations of predisposing, enabling and need characteristics on the odds of bevacizumab use among patients receiving platinum-taxane doublet chemotherapy

Characteristic	Adjusted OR	95% CI	p-value
Predisposing			
Age			0.278
66 to 69	ref		
70 to 79	0.93	(0.69, 1.25)	
80 and older	0.69	(0.44, 1.09)	
Sex			0.966
Female	ref		
Male	1.01	(0.77, 1.32)	
Marital status			0.429
Not married	ref		
Married	1.12	(0.84, 1.50)	
Race			0.549
White	ref		
Black	0.95	(0.53, 1.69)	
Other	1.39	(0.76, 2.54)	
% 25 years and older in census tract w/ < HS education			0.425
Lowest quartile	ref		
Second	0.77	(0.53, 1.13)	
Third	0.70	(0.45, 1.09)	
Highest	0.76	(0.44, 1.31)	
Enabling			
Median household income (census tract level)			0.823
Lowest quartile	ref		
Second	0.94	(0.59, 1.49)	
Third	0.83	(0.49, 1.42)	
Highest	0.97	(0.53, 1.75)	
Population density			0.332
Urban/Rural	ref		
Metro	1.24	(0.81, 1.89)	
State buy-in Medicare coverage during year preceding diagnosis			0.599
No	ref		
Yes	0.87	(0.51, 1.47)	
≥ 50% of chemotherapy claims from CCOP provider			0.002
No	ref		
Yes	1.60	(1.19, 2.15)	
Year of diagnosis			<0.001
2004-2005	ref		
2006	8.97	(5.97, 13.47)	
2007	14.14	(9.44, 21.17)	

Table 4.7 (Continued)

SEER region			0.207
East	Ref		
Midwest	1.35	(0.86, 2.12)	
South	1.50	(1.02, 2.19)	
West	1.43	(0.93,2.20)	
Need			
Tumor stage			0.004
IIIB	Ref		
IV	1.70	(1.19, 2.42)	
Summary stage			0.214
Regional	Ref		
Distant	1.59	(0.76, 3.33)	
Grade			0.655
Well/Moderately differentiated	Ref		
Poor/Undifferentiated	0.96	(0.60, 1.53)	
Unknown	1.10	(0.72, 1.68)	
Histology			0.029
Adenocarcinoma	Ref		
Large cell	0.56	(0.27, 1.18)	
Other and NOS	0.71	(0.53, 0.94)	
NCI Charlson Comorbidity Index			0.005
0	Ref		
1	0.73	(0.55, 0.97)	
2	0.31	(0.13, 0.73)	
Hemoptysis			0.0881
No	Ref		
Yes	0.51	(0.23, 1.11)	
Brain metastases			0.024
No	Ref		
Yes	0.67	(0.48, 0.95)	
Radiation therapy received			<0.001
No	Ref		
Yes	0.37	(0.28, 0.49)	
Cancer-directed surgery			0.044
No	Ref		
Yes	0.48	(0.24, 0.98)	

Abbreviations: OR = Odds ratio; CI = Confidence interval; CCOP = Clinical Community Oncology Program; NOS = Not otherwise specified; NCI = National Cancer Institute

4.3.2.3 Hierarchical multivariate regression analysis

A hierarchical regression model was constructed as part of a sensitivity analysis to assess for changes in the association between predisposing, enabling, and need characteristics and the use of bevacizumab. The hierarchical analysis was conducted by first including only the predisposing variables in a logistic regression model to evaluate their associations with the use of bevacizumab. Subsequent regression models were then performed, first adding enabling and then need characteristic variables, to evaluate their associations with the use of bevacizumab, controlling for the prior variables in the model. No significant differences were found between the results of the hierarchical analysis and the results of the multivariate analysis described above. As such, the results of the multivariate regression models for predisposing characteristics, and predisposing and enabling characteristics are described individually within tables of Appendix B. In addition, hierarchical analysis results among patients who specifically received a platinum-taxane doublet regimen are described separately for each model.

4.4 Aim 2: Survival Analysis

Aim 2 was designed to determine whether the utilization of bevacizumab in addition to standard platinum-based doublet chemotherapy as first-line treatment of older adults with advanced NSCLC is associated with a benefit of improved overall survival. Analysis of survival was performed through the estimation of the hazard of death among patients who received bevacizumab in combination with platinum-based doublet chemotherapy relative to those patients who received platinum-based doublet chemotherapy only. In addition, the odds of one-year survival following the initiation of treatment was estimated and compared between patients who received bevacizumab with platinum-based doublet chemotherapy and those patients who received platinum-based doublet chemotherapy only. Furthermore, additional analyses of overall survival duration and one-year survival were performed for those patients who received first-line treatment with a platinum-taxane doublet regimen specifically.

4.4.1 Bivariate analysis of the use of bevacizumab and survival

Figure 4.3 describes the median survival times and unadjusted hazard ratios (HR) comparing the hazard of death among patients who received bevacizumab in combination with platinum-based doublet chemotherapy relative to those patients who received platinum-based doublet chemotherapy only. Survival duration was similar between those patients who received bevacizumab and those patients who did not. Among patients who received first-line treatment with any platinum-based doublet chemotherapy, those who also received bevacizumab had a median survival duration of 9.8 months while those who did not had a median survival duration of 8.9 months (HR 1.02, 95% CI 0.91-1.13; p-value = 0.76). Among those who were specifically treated with a platinum-taxane doublet (Figure 4.4), the median survival duration was 10.0 months for patients receiving bevacizumab and 9.0 months for patients receiving chemotherapy only (HR 1.01, 95% CI 0.89-1.13;

p-value = 0.89), further indicating that bevacizumab provided not additional benefit with respect to improving overall survival.

Visual evaluation of the Kaplan-Meier survival plots detected a crossing of the survival curves for the two treatment groups, representing a potential violation of the proportional hazards assumption and thus a concern for the appropriate interpretation of effect estimates from Cox proportional hazards models. The proportionality of the survival curves was investigated further by testing for the interaction between bevacizumab and the log of survival time within Cox proportional hazards models (statistical significance of a time-dependent covariate suggests the survival curves for the predictor are non-proportional). However, in each cohort (i.e., any platinum-based doublet and platinum-taxane doublet), the interaction term for bevacizumab and the log of survival time was not statistically significant in the Cox proportional hazards models, implying the proportional hazards assumption was not violated.

Figure 4.3 Kaplan-Meier survival curves according to the use of bevacizumab among patients receiving any platinum-based doublet chemotherapy

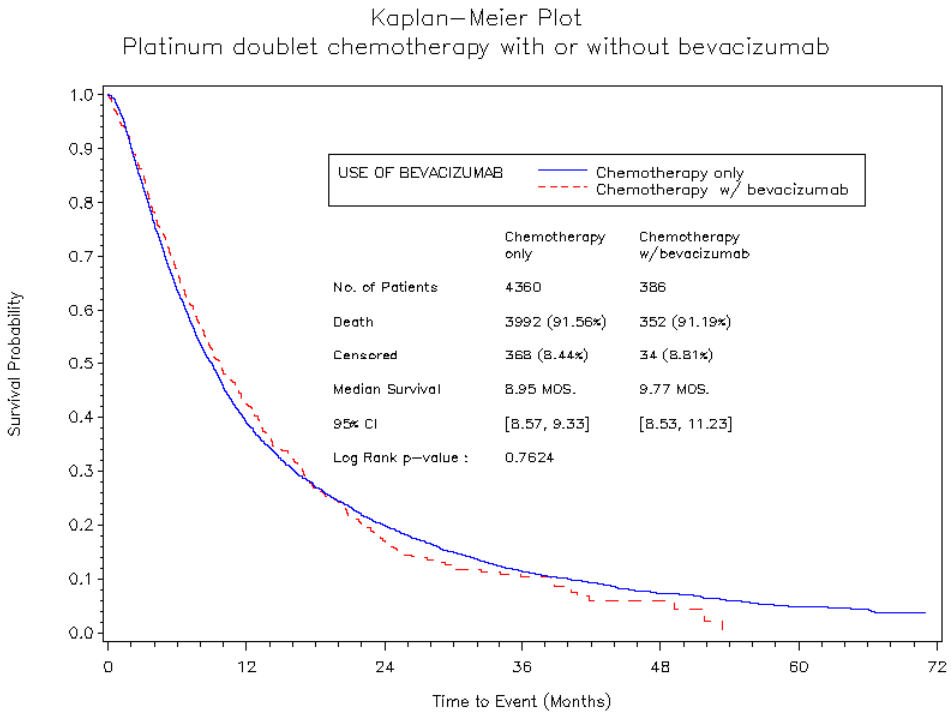


Figure 4.4 Kaplan-Meier survival curves according to the use of bevacizumab among patients receiving platinum-taxane doublet chemotherapy

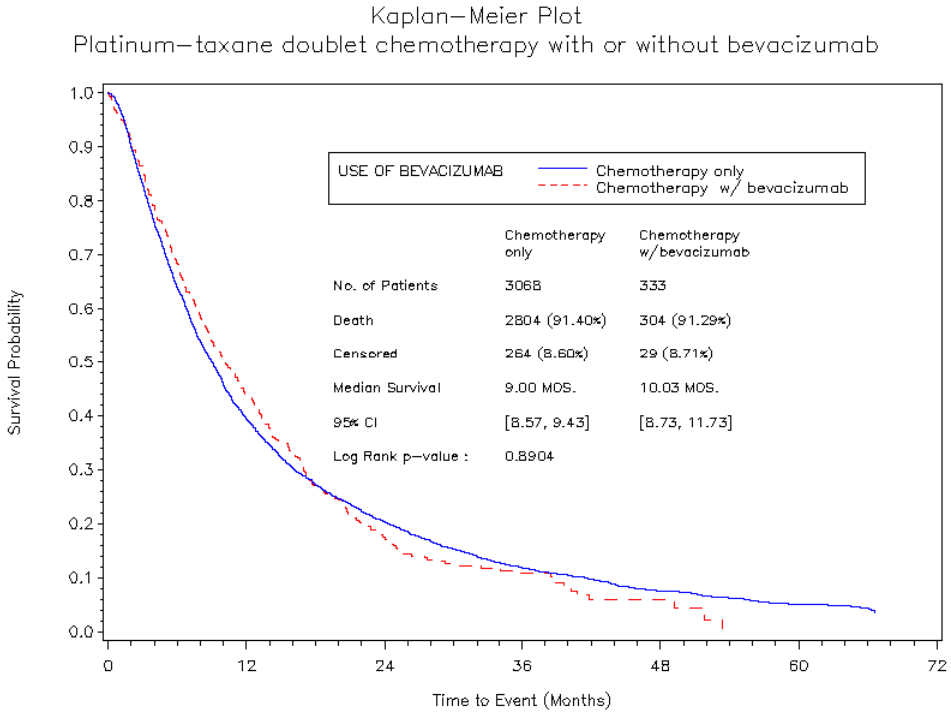


Table 4.8 displays the results for one-year survival based on the use of bevacizumab. One-year survival was determined using the time between the first date of treatment and the date of death reported by Medicare, with patients who were alive at least 365 days following the start of treatment considered one-year survivors. Among patients who received any platinum-based doublet regimen, 42.0% of patients who received bevacizumab and 38.7% of patients who did not survived one year or longer. In comparing the two groups, the estimated odds of surviving one year following the start of treatment was greater among patients who received bevacizumab than among those patients who did not (OR 1.15, 95% CI 0.93-1.42), but this finding was not statistically significant. Examining patients who specifically received treatment with platinum-taxane doublet regimens yielded similar results. Patients who received platinum-taxane doublet chemotherapy with bevacizumab had approximately 21% greater odds of surviving at least one year from the start of treatment as compared to patients

who received platinum-taxane chemotherapy only, but this result also was not statistically significant (OR 1.21, 95% 0.96-1.51).

Table 4.8 One-year survival by receipt of bevacizumab

Treatment	Patients treated, n	Patients surviving ≥ 1-year, n (%)	OR (95% CI)
Any platinum-based doublet chemotherapy			
without bevacizumab	4360	1687 (38.7)	ref
with bevacizumab	386	162 (42.0)	1.15 (0.93, 1.42)
Platinum-taxane doublet chemotherapy			
without bevacizumab	3068	1197 (39.0)	ref
with bevacizumab	333	145 (43.5)	1.21 (0.96, 1.51)

Abbreviations: OR = Odds ratio; CI = Confidence interval

4.4.2 Bivariate analysis of survival and predisposing, enabling, and need characteristics

Bivariate associations between overall survival duration and predisposing, enabling, and need characteristics were evaluated to identify variables that may confound the relationship between survival and the use of bevacizumab. Results are shown in Table 4.9.

Predisposing characteristics

Overall, age was not a significant predictor of survival among patients treated with platinum-based doublet chemotherapy. However, when compared to patients aged 66 to 69, patients 80 and older had significantly poorer survival (HR 1.12, 95% CI 1.01-1.24); patients aged 70 to 79 also had an increased hazard of death in comparison to patients aged 66 to 69, but this finding was not statistically significant (HR 1.06, 95% CI 0.99-1.14). Both race and the census tract measure for education were significant bivariate predictors of overall survival in this cohort of patients receiving platinum-based doublet chemotherapy. For example, the hazard of death was significantly lower among patients of 'other' race in comparison to white patients (HR 0.76, 95% CI 0.66-0.87) while the

hazard of death was significantly higher among patients residing in census tract areas with higher percentages of residents with less than a high school education (highest vs. lowest quartile: HR 1.18, 95% CI 1.08-1.29). Among additional predisposing characteristics, sex was a significant predictor of overall survival among patients receiving platinum-based doublet chemotherapy; the hazard of death was significantly higher among males as compared to females (HR 1.29, 95% CI 1.21-1.37). Conversely, there was little difference in survival between married and non-married patients.

Enabling variables

In addition to education, the socioeconomic status measure of median household income was also associated with overall survival; specifically, the hazard of death was significantly lower among patients residing in census tract areas of higher median household income (highest vs. lowest quartile: HR 0.90, 95% CI 0.83-0.99). Although provider affiliation with the CCOP was positively associated with the utilization of bevacizumab, there was no apparent relationship between provider CCOP-affiliation and overall survival as the hazard of death was nearly equal between patients who received at least 50% of chemotherapy from a CCOP-affiliated provider and patients who did not. Among additional enabling characteristics, the hazard of death was significantly lower in patients receiving treatment from a provider affiliated with a cooperative research group (HR 0.90, 95% CI 0.85-0.96). A statistically significant difference in the hazard of death was also found for SEER region based on the result of significantly greater survival in patients from the West region compared to patients from the Midwest region (HR 0.87, 95% CI 0.79-0.96; not shown in table).

Need variables

Several need characteristics were also significantly associated with overall survival, including tumor stage, tumor grade, tumor histology, NCI Charlson comorbidity index score, the presence of brain metastases, receipt of radiation treatment, and receipt of any cancer-directed surgery. In regards to tumor characteristics, overall survival was significantly poorer among patients diagnosed with

stage IV disease compared to patients diagnosed with stage IIIB (HR 1.50, 95% CI 1.40-1.60), patients with poor/undifferentiated (HR 1.48, 95% CI 1.33-1.65) or unknown (HR 1.41, 95% CI 1.31-1.56) tumor grade compared to patients with well/moderately differentiated tumors, patients with large cell (HR 1.17, 95% CI 1.03-1.34) or other/not otherwise specified (HR 1.12, 95% CI 1.05-1.19) histology compared to patients with adenocarcinoma. Patients with an NCI Charlson comorbidity index of 1 or 2 each had significantly higher hazards of death compared to patients with an index of 0 and the hazard of death was significantly greater among patients with brain metastases compared to those without (HR 1.17, 95% CI 1.09-1.25). Lastly, patients who received radiation treatment had significantly poorer survival compared to those who did not (HR 1.09, 95% CI 1.03-1.16), whereas patients who received cancer-directed surgery had significantly better survival in comparison to patients who did not have any surgery (HR 0.50, 95% CI 0.44-0.57).

Bivariate associations between overall survival duration and predisposing, enabling, and need characteristics were also evaluated among patients who specifically received platinum-taxane doublet chemotherapy. Results of this analysis were nearly identical to those previously described (Appendix C: Table C-1).

Table 4.9 Bivariate associations between overall survival and predisposing, enabling, and need characteristics among patients receiving platinum-based doublet chemotherapy

		Median survival time		
Characteristic	**No. of patients**	**Months (95% CI)**	**Log-rank p-value**	**HR (95% CI)**
Predisposing				
Age at diagnosis			0.065	
66 to 69	1260	9.4 (8.8, 10.0)		ref
70 to 79	2878	8.9 (8.4, 9.4)		1.06 (0.99, 1.14)
80 and older	608	8.7 (7.8, 9.5)		1.12 (1.01, 1.24)
Sex			< 0.001	
Female	2232	10.3 (9.8, 10.8)		ref
Male	2514	8.0 (7.5, 8.4)		1.29 (1.21, 1.37)

Table 4.9 (Continued)

Marital Status			0.340	
Not married	1809	8.8 (8.1, 9.3)		ref
Married	2937	9.1 (8.7, 9.6)		0.97 (0.91, 1.03
Race			< 0.001	
White	4219	8.8 (8.5, 9.2)		ref
Black	288	9.4 (7.9, 10.5)		0.97 (0.86, 1.10)
Other	239	14.0 (10.1, 15.9)		0.76 (0.66, 0.87)
% 25 years and older in census tract w/ < HS education			0.001	
Lowest quartile	1339	9.5 (8.7, 10.2)		ref
Second	1241	9.1 (8.5, 9.8)		1.08 (0.99, 1.17)
Third	1198	8.8 (7.8, 9.5)		1.12 (1.03, 1.22)
Highest	959	8.7 (7.8, 9.4)		1.18 (1.08, 1.29)
Enabling				
Median household income (census tract level)			0.003	
Lowest quartile	977	9.2 (8.5, 9.9)		ref
Second	1181	8.5 (7.8, 9.1)		1.05 (0.96, 1.15)
Third	1224	8.7 (8.0, 9.4)		1.00 (0.91, 1.09)
Highest	1365	9.7 (9.0, 10.4)		0.90 (0.83, 0.99)
Population density			0.178	
Urban/rural	689	9.2 (8.4, 10.0)		ref
Metro	4057	9.0 (8.6, 9.4)		0.94 (0.87, 1.03)
State buy-in Medicare coverage during year preceding diagnosis			0.622	
No	4330	9.0 (8.7, 9.4)		ref
Yes	416	8.8 (7.5, 9.9)		0.97 (0.88, 1.08)
≥ 50% of chemotherapy claims from CCOP provider			0.405	
No	3541	8.8 (8.4, 9.2)		ref
Yes	1025	9.3 (8.7, 9.9)		0.97 (0.90, 1.04)
Received treatment from provider affiliated with a cooperative research group			0.001	
No	1965	8.3 (7.7, 8.8)		ref
Yes	2445	9.4 (8.8, 9.9)		0.90 (0.85, 0.96)
Year of diagnosis			0.216	
2004-2005	2378	8.6 (8.2, 9.1)		ref
2006	1242	9.5 (8.8, 10.2)		0.94 (0.87, 1.01)
2007	1126	9.3 (8.7, 10.0)		0.98 (0.90, 1.05)

Table 4.9 (Continued)

SEER region			0.046	
East	1107	9.4 (8.5, 9.9)		ref
Midwest	893	8.2 (7.3, 9.0)		1.09 (0.99, 1.20)
South	1896	8.8 (8.3, 9.4)		1.02 (0.94, 1.10)
West	950	9.7 (9.0, 10.5)		0.95 (0.87, 1.04)
Need				
Tumor stage			< 0.001	
IIIB	1380	12.6 (11.8, 13.6)		ref
IV	3366	7.7 (7.4, 8.2)		1.50 (1.40, 1.60)
Summary stage			< 0.001	
Regional	410	15.4 (13.2, 17.8)		ref
Distant	4335	8.6 (8.2, 8.9)		1.64 (1.47, 1.83)
Grade			< 0.001	
Well/Moderate	543	12.3 (10.8, 14.3)		ref
Poor/Undifferentiated	1382	8.1 (7.5, 8.7)		1.48 (1.33, 1.65)
Unknown	2821	9.0 (8.5, 9.4)		1.41 (1.28, 1.56)
Tumor histology			< 0.001	
Adenocarcinoma	2642	9.6 (9.1, 10.0)		ref
Large cell	256	7.7 (6.1, 9.5)		1.17 (1.03, 1.34)
Other and NOS	1848	8.3 (7.9, 8.8)		1.12 (1.05, 1.19)
NCI Charlson Comorbidity Index			< 0.001	
0	2814	9.5 (8.9, 9.9)		ref
1	1580	8.7 (8.2, 9.3)		1.11 (1.04, 1.18)
2	235	6.9 (5.6, 8.5)		1.43 (1.25, 1.64)
Hemoptysis			0.634	
No	4550	9.0 (8.6, 9.4)		ref
Yes	196	9.1 (7.7, 10.1)		0.96 (0.83, 1.12)
Brain metastases			< 0.001	
No	3625	9.1 (8.6, 9.4)		ref
Yes	1121	8.9 (8.3, 9.5)		1.17 (1.09, 1.25)
Radiation therapy received			0.004	
No	2366	9.7 (9.2, 10.2)		ref
Yes	2314	8.4 (8.0, 8.8)		1.09 (1.03, 1.16)
Cancer-directed surgery			< 0.001	
No	4404	8.7 (8.3, 9.0)		ref
Yes	321	18.7 (14.7, 22.9)		0.50 (0.44, 0.57)

Abbreviations: CI = Confidence interval; HR = Hazard ratio; CCOP = Clinical Community Oncology Program; SEER = Surveillance, Epidemiology, and End Results; NOS = Not otherwise specified; NCI = National Cancer Institute.

4.4.3 Multivariate analysis of bevacizumab and survival

Multivariate Cox proportional hazards models were used to evaluate the effect of bevacizumab on overall survival while adjusting for potential confounders. Several different hazards models were constructed, selecting clinical, sociodemographic, and health care system variables based on Andersen's Behavioral Model of Health Services Use and/or their significant bivariate associations with survival. Results from the multivariate Cox proportional hazards models evaluating the effect of bevacizumab on overall survival among patients who received any platinum-based doublet chemotherapy as well as among those who specifically received platinum-taxane doublet chemotherapy are presented in Table 4.10.

Table 4.10 Effect of adding bevacizumab to platinum-based doublet chemotherapy on hazard ratios for overall survival

	Any platinum doublet			Platinum-taxane doublet		
	Sample, n			Sample, n		
	Bevacizumab			Bevacizumab		
Models	**Yes**	**No**	**HR (95% CI)**	**Yes**	**No**	**HR (95% CI)**
Unadjusted	386	4360	1.02 (0.91, 1.13)	333	3068	1.01 (0.89, 1.13)
Multivariate-adjusted						
Predisposing[a]	386	4351	1.04 (0.93, 1.16)	333	3062	1.04 (0.92, 1.16)
Enabling[b]	366	4040	1.04 (0.93, 1.17)	319	2832	1.03 (0.90, 1.17)
Need[c]	364	4200	0.96 (0.85, 1.07)	313	2956	0.95 (0.84, 1.08)
Predisposing & enabling	366	4031	1.07 (0.95, 1.20)	319	2826	1.06 (0.93, 1.20)
Predisposing, enabling, & need	346	3890	1.00 (0.89, 1.13)	300	2729	0.99 (0.87, 1.13)
Identified confounders[d,e]	346	3890	0.96 (0.86, 1.08)	300	2736	0.95 (0.84, 1.08)

Table 4.10 (Continued)

Propensity score-adjusted[f,g]						
Covariate adjustment	333	3890	1.03 (0.91, 1.16)	300	2736	1.00 (0.87, 1.14)
Matching[h]	346	346	0.94 (0.78, 1.16)	300	300	0.99 (0.83, 1.20)

[a] The model was adjusted for age, sex, marital status, race, and census tract level of education
[b] The model was adjusted for census tract level of median household income, population density, state buy-in Medicare coverage during year preceding diagnosis, ≥ 50% of chemotherapy from provider affiliated with the Community Clinical Oncology Program, treatment from a provider affiliated with a cooperative research group, year of diagnosis, and SEER region
[c] The model was adjusted for stage at diagnosis, tumor grade, histology, NCI Charslon comorbidity index, hemoptysis, brain metastases, radiation, and cancer-directed surgery
[d] The model for patients receiving any platinum-based doublet was adjusted for sex, race, census tract level of education, census tract level of median household income, treatment from a provider affiliated with a cooperative research group, SEER region, stage at diagnosis, tumor grade, histology, NCI Charslon comorbidity index, brain metastases, radiation, and cancer-directed surgery
[e] The model for patients receiving platinum-taxane doublet chemotherapy was adjusted for sex, race, treatment from a provider affiliated with a cooperative research group, stage at diagnosis, tumor grade, histology, NCI Charslon comorbidity index, brain metastases, radiation, and cancer-directed surgery
[f] The propensity of receiving bevacizumab was estimated among patients who received any platinum-based doublet using a multivariable logistic regression model that included sex, race, census tract level of education, census tract level of median household income, treatment from a provider affiliated with a cooperative research group, SEER region, stage at diagnosis, tumor grade, histology, NCI Charslon comorbidity index, brain metastases, radiation, and cancer-directed surgery
[g] The propensity of receiving bevacizumab was estimated among patients who received a platinum-taxane doublet using a multivariable logistic regression model that included sex, race, treatment from a provider affiliated with a cooperative research group, SEER region, stage at diagnosis, tumor grade, histology, NCI Charslon comorbidity index, brain metastases, radiation, and cancer-directed surgery
[h] Using a greedy match algorithm, patients receiving platinum-based chemotherapy only were matched on estimated propensity scores to patients receiving platinum-based chemotherapy with bevacizumab
Abbreviations: HR = Hazard ratio; CI = Confidence interval; SEER = Surveillance, Epidemiology, and End Results; NCI = National Cancer Institute.

4.4.3.1 Multivariate adjustment: predisposing, enabling, and need characteristics

Overall, bevacizumab did not have any significant effect on survival in the Cox proportional hazards models that adjusted for clinical, sociodemographic, and health care system variables categorized based on Andersen's Behavioral Model of Health Services Use. However, the estimated hazard ratio (HR) fell on either side of the null value, depending on which covariates were included in the regression model. For example, when predisposing characteristics, enabling characteristics, or both were controlled for, the estimated hazard ratios were 1.04, 1.04, and 1.07, respectively. Conversely, when need characteristics were controlled for in addition to predisposing and enabling characteristics, the estimated HR was approximately 1.00 (95% CI 0.89-1.13) and when need

characteristics alone were controlled for, the estimated HR was 0.96 (95% CI 0.85-1.07). Results from the Cox hazards models that adjusted for clinical, sociodemographic, and health care system variables categorized based on Andersen's Behavioral Model of Health Services Use among patients who specifically received platinum-taxane doublet chemotherapy were similar to those seen among patients who received any platinum-based doublet chemotherapy. In addition, full results from multivariable Cox proportional hazards models estimating the effects of bevacizumab and each of the predisposing, enabling, and need characteristics on overall survival are included in Appendix D (Table D-1); briefly, need characteristics including AJCC stage, tumor grade, and comorbidity score at the time of diagnosis remained significant independent predictors of overall survival, irrespective of treatment received.

4.4.3.2 Multivariate adjustment: variables with bivariate associations with overall survival

Additional multivariable Cox proportional hazards models were constructed in which covariates were selected based on significant bivariate associations with overall survival. Among patients who received any platinum-based doublet chemotherapy, the Cox hazards model included sex, race, census tract level of education, census tract level of median household income, treatment from a provider affiliated with a cooperative research group, SEER region, AJCC stage at diagnosis, tumor grade, histology, NCI Charlson comorbidity index, brain metastases, radiation, and cancer-directed surgery. The Cox hazards model among patients who specifically received platinum-taxane doublet chemotherapy was similar, but did not include SEER region or the census tract level variables as these were not significantly associated with overall survival in this subgroup of patients. Results from these multivariable Cox hazards models again show that bevacizumab did not have a significant effect on overall survival, even after adjusting for identified confounders. The hazard ratios and confidence intervals, both among patients who received any platinum-based doublet (HR 0.96, 95% CI 0.86-1.08) and among those who received a platinum-taxane doublet (HR 0.95, 95% CI 0.84-

1.08), are nearly identical to those seen in the multivariable-adjusted models that contained only need characteristics, which is likely due to the similarities in the covariates included in each of the models.

4.4.3.3 Propensity score adjustment

In addition to the multivariable-adjusted survival analyses, Cox proportional hazards models were also constructed using estimated propensity scores. Initially, propensity score analysis was performed to balance measured confounders between patients who received chemotherapy with bevacizumab and patients who received platinum-based chemotherapy only. Of note, identified confounders differed between patients receiving any platinum-based doublet chemotherapy and patients receiving platinum-taxane chemotherapy specifically, therefore, distinct propensity scores were calculated for each cohort of patients.

Multivariate logistic regression models were first used to calculate propensity scores representing the probability that a patient received bevacizumab conditional on all other measured confounders in the model. In each propensity score model, variables that were associated with bevacizumab use and overall survival (true confounders) as well as variables related to overall survival only were included. For the cohort of patients receiving any platinum-based doublet chemotherapy, the propensity score model included sex, race, census tract level of education, census tract level of median household income, treatment from a provider affiliated with a cooperative research group, SEER region, AJCC stage at diagnosis, tumor grade, histology, NCI Charslon comorbidity index, brain metastases, radiation, and cancer-directed surgery as confounders. The model used to derive propensity scores in the cohort of patients receiving platinum-taxane chemotherapy included sex, race, treatment from a provider affiliated with a cooperative research group, SEER region, AJCC stage at diagnosis, tumor grade, histology, NCI Charslon comorbidity index, brain metastases, radiation, and cancer-directed surgery.

Following propensity score estimation, the propensity scores were applied to Cox proportional hazards models to perform two distinct propensity score-adjusted analyses. In the first propensity score-adjusted analysis, discrete Cox PH regression models were fit using the propensity score as a continuous covariate in the regression model. In the second propensity score-adjusted analysis, propensity score estimates were used to first match exposed patients (receiving bevacizumab) to patients from the unexposed group (receiving chemotherapy only) in a 1:1 ratio using a 5-to-1 digit greedy-match algorithm. The algorithm allows for the capture of the best possible matches (those pairs matched to the fifth digit of the PS) while also maximizing the number of possible matches by including pairs matched to the fourth, third, second, and first digits of the PS (adequacy of the matches decrease with the number of digits matched on); non-matched individuals are excluded from the derived cohort of matched patients. Application of the 1:1 greedy-match algorithm resulted in 346 matched pairs among patients receiving any platinum-based doublet chemotherapy and 300 matched pairs among patients receiving platinum-taxane doublet chemotherapy specifically.

After deriving the matched cohort, Chi-square tests were used to assess for even balance of measured covariates across the groups of matched patients; uneven balance of the covariates across groups may signal a poor propensity score model and/or the need to include unbalanced covariates as independent variables in subsequent regression models evaluating treatment effects. In this study, Chi-square test results showed that, with the exception of age, marital status at diagnosis, hemoptysis, and year of diagnosis among patients receiving any platinum-based doublet chemotherapy and year of diagnosis only among patients receiving platinum-taxane chemotherapy, measured covariates were evenly distributed between patients who received chemotherapy with bevacizumab and propensity score-matched patients who received chemotherapy only (Appendix E: Table E-1); age, marital status, hemoptysis, and year of diagnosis were thus included as additional covariates in the propensity score models assessing the effect of bevacizumab on survival among patients receiving any platinum-based doublet chemotherapy and year of diagnosis was included in the models among patients

receiving platinum-taxane regimens in particular. Following the evaluation of covariate balance across matched treatment groups, discrete Cox PH regression models were then fit to estimate the effect of bevacizumab on overall survival among the cohort of matched patients; patients who were not matched were excluded from this analysis.

Overall, bevacizumab did not have a significant effect on survival in any of the propensity score-adjusted models. Among patients who received any platinum-based doublet and among patients who received platinum-taxane regimens in particular, the estimated hazards ratios and confidence intervals for the use of bevacizumab were similar to the unadjusted estimates and were slightly higher than those seen in the multivariable models that adjusted for covariates with significant bivariate associations with overall survival. In the samples of patients matched on estimated propensity scores, the estimated hazards ratio for the effect of bevacizumab on survival were lower than unadjusted estimates among patients who received any platinum-based doublet (HR 0.94, 95% CI 0.78-1.12) and among patients who received platinum-taxane regimens (HR 0.99, 95% CI 0.83-1.20) in particular, but neither result was statistically significant.

4.4.3.4 Subgroup analyses

Subgroup analysis of the effect of bevacizumab on overall survival was performed for patients diagnosed with stage IV disease. In addition to an unadjusted model, a multivariable Cox proportional hazards model was constructed for the subgroup and included covariates with significant bivariate associations with overall survival. The results from the subgroup analysis of patients diagnosed with stage IV NSCLC are shown in Table 4.11. The unadjusted hazards ratios for bevacizumab among patients with stage IV disease were lower than the unadjusted hazards ratios that were estimated among all patients who received any platinum-based doublet chemotherapy or received platinum-taxane chemotherapy specifically. Adjusting for confounders in multivariable Cox proportional hazards models lowered the resulting estimated hazards ratios among patients who

receive any platinum-based doublet chemotherapy (HR 0.92, 95% CI 0.80-1.03) and among patients who received platinum-taxane chemotherapy in particular (HR 0.92, 95% CI 0.80-1.06). Although the estimated hazards ratios slightly favored the use of bevacizumab, the estimated effect of bevacizumab on overall survival was not statistically significant among patients diagnosed with stage IV disease.

Table 4.11 Effect of adding bevacizumab to platinum-based doublet chemotherapy on hazard ratios for overall survival among patients diagnosed with stage IV disease

	Any platinum doublet Sample, n Bevacizumab			Platinum-taxane doublet Sample, n Bevacizumab		
Models	**Yes**	**No**	**HR (95% CI)**	**Yes**	**No**	**HR (95% CI)**
Unadjusted	312	3054	0.91 (0.80, 1.03)	270	2111	0.90 (0.79, 1.03)
Multivariate-adjusted[a,b]	282	2723	0.92 (0.81, 1.05)	247	1885	0.92 (0.80, 1.06)

[a] The model for patients receiving any platinum-based doublet was adjusted for sex, race, census tract level of education, census tract level of median household income, treatment from a provider affiliated with a cooperative research group, SEER region, tumor grade, histology, NCI Charslon comorbidity index, brain metastases, radiation, and cancer-directed surgery

[b] The model for patients receiving platinum-taxane doublet chemotherapy was adjusted for sex, race census tract level of median household income, treatment from a provider affiliated with a cooperative research group, tumor grade, histology, NCI Charslon comorbidity index, radiation, and cancer-directed surgery

Abbreviations: HR = Hazard ratio; CI = Confidence interval; SEER = Surveillance, Epidemiology, and End Results; NCI + National Cancer Institute.

4.4.3.5 Sensitivity analyses

Finally, two separate sensitivity analyses were conducted. The first sensitivity analysis assessed for changes in the effect estimate of bevacizumab on overall survival when the interval for identifying the concurrent use of bevacizumab with platinum-based doublet chemotherapy was expanded from 8 to 30 days. In this analysis, patients who had a Medicare claim for bevacizumab within 30 days of chemotherapy initiation were considered to have received bevacizumab in addition to platinum-based doublet chemotherapy and all other patients were considered to have received platinum-based doublet chemotherapy only. The second sensitivity analysis assessed for the potential impact of immortal time bias on the effect estimate of bevacizumab on overall survival. In this analysis survival time was measured as the number of days starting from the first day after the end of

the treatment identification interval (Day 9 for the 8 day interval and Day 31 for the 30 days interval) to the time of death or censoring, whichever occurred first.

Expansion of treatment identification interval from 8 days to 30 days

Table 4.12 displays results of the sensitivity analysis exploring the impact of increasing the interval for identifying the concurrent use of bevacizumab with platinum-based doublet chemotherapy from 8 days to 30 days. In each of the Cox proportional hazards models, extension of the interval to identify the utilization of bevacizumab from 8 days to 30 days resulted in a decrease in the estimated hazards ratio. For example, among patients who received platinum-taxane doublet chemotherapy, the unadjusted hazards ratio for the effect of bevacizumab on overall survival was 1.01 (95% CI 0.89-1.13) using the 8-day interval compared to 0.97 (95% CI 0.86-1.08) using the 30-day interval. However, consistent with results from the primary analyses, bevacizumab was not significantly associated with overall survival in any of the Cox proportional hazards models even after extending the interval to identify the use of bevacizumab from 8 days to 30 days.

Table 4.12 Impact of increasing the interval for identifying the concurrent use of bevacizumab with platinum-based doublet chemotherapy (from 8 days to 30 days) on the estimated effect of bevacizumab on survival

	Any platinum doublet[a] Sample, n			Platinum-taxane doublet[b] Sample, n		
	Bevacizumab			Bevacizumab		
Models	**Yes**	**No**	**HR (95% CI)**	**Yes**	**No**	**HR (95% CI)**
8-day interval						
Unadjusted model	386	4360	1.02 (0.91, 1.13)	333	3068	1.01 (0.89, 1.13)
Multivariate-adjusted model	346	3890	0.96 (0.86, 1.08)	300	2736	0.95 (0.84, 1.08)
30-day interval						
Unadjusted model	456	4290	0.97 (0.88, 1.07)	389	3012	0.97 (0.86, 1.08)
Multivariate-adjusted model	409	3827	0.93 (0.83, 1.04)	351	2685	0.92 (0.81, 1.03)

[a] Multivariate models adjusted for sex, race, census tract levels of education and median household income, treatment from a provider affiliated with a cooperative research group, SEER region, stage at diagnosis, tumor grade, histology, NCI Charslon comorbidity index, brain metastases, radiation, and cancer-directed surgery

[b] Multivariate models adjusted for sex, race, treatment from a provider affiliated with a cooperative research group, stage at diagnosis, tumor grade, histology, NCI Charslon comorbidity index, brain metastases, radiation, and cancer-directed surgery

Abbreviations: HR = Hazard ratio; CI = Confidence interval; Surveillance, Epidemiology, and End Results; NCI = National Cancer Institute.

Measurement of survival starting after the end of the treatment identification interval

Results of the sensitivity analysis investigating the influence of immortal time bias on the effect estimates for bevacizumab on overall survival are presented in Table 4.13. Measuring survival starting on Day 9 (the first day following the 8-day interval used to identify concurrent use of bevacizumab with platinum-based doublet chemotherapy) had little influence on the estimated hazards ratio. Both the unadjusted and adjusted hazards models among patients who received any platinum-based doublet or platinum-taxane doublet chemotherapy yielded effect estimates that were nearly identical to those seen in the same models when survival was measured starting the first date of treatment. For example, among patients who received platinum-taxane chemotherapy, the multivariable-adjusted model measuring survival on Day 9 and the corresponding model measuring survival on Day 1 both produced an estimated hazard ratio of 0.95 (95% CI: Day 1, 0.84-1.08; Day 9, 0.83-1.07) . Measuring survival starting on Day 31 (the first day following the alternative 30-day interval to identify concurrent use of bevacizumab) also had little influence on the estimated hazards ratio. Similar to the results just described, effect estimates in both the unadjusted and multivariable-adjusted hazards models were comparable to those seen in the same models when survival was measured starting the first date of treatment. To illustrate, using an interval of 30 days to identify the use of bevacizumab among patients who received platinum-taxane chemotherapy, the multivariable-adjusted model measuring survival on Day 31 produced an estimated hazard ratio of 0.90 (95% CI 0.79-1.01) and the corresponding model measuring survival on Day 1 yielded an estimated hazard ratio of 0.92 (95% CI 0.81-1.03).

Table 4.13 Estimated effect of bevacizumab on survival when the measure of survival is initiated at the end of the interval used to identify bevacizumab treatment

	Any platinum doublet[a] Sample, n			Platinum-taxane doublet[b] Sample, n		
	Bevacizumab			Bevacizumab		
Models	**Yes**	**No**	**HR (95% CI)**	**Yes**	**No**	**HR (95% CI)**
8-day interval						
Unadjusted model	383	4353	1.01 (0.90, 1.12)	330	3064	1.00 (0.89, 1.12)
Multivariate-adjusted model	343	3886	0.96 (0.85, 1.07)	297	2733	0.95 (0.83, 1.07)
30-day interval						
Unadjusted model	440	4177	0.96 (0.87, 1.06)	374	2937	0.95 (0.85, 1.06)
Multivariate-adjusted model	394	3729	0.92 (0.82, 1.03)	337	2618	0.90 (0.79, 1.01)

[a] Multivariate models adjusted for sex, race, census tract level of education, census tract level of median household income, treatment from a provider affiliated with a cooperative research group, SEER region, AJCC stage at diagnosis, tumor grade, histology, NCI Charslon comorbidity index, brain metastases, radiation, and cancer-directed surgery

[b] Multivariate models adjusted for sex, race, cooperative research group, AJCC stage at diagnosis, tumor grade, histology, NCI Charslon comorbidity index, brain metastases, radiation, and cancer-directed surgery

Abbreviations: HR = Hazard ratio; CI = Confidence interval; Surveillance, Epidemiology, and End Results; NCI = National Cancer Institute.

4.4.4 Summary of survival analysis

No significant survival benefit was found with the concurrent use of bevacizumab and platinum-based doublet chemotherapy compared to platinum-based doublet chemotherapy alone. Controlling for confounding variables through the use of multivariable-adjusted and propensity score-adjusted models resulted in lower estimated hazard ratios (favoring the use of bevacizumab) compared to unadjusted models, but the findings were not statistically significant. A subgroup analysis evaluating treatment effects among patients with stage IV disease, and sensitivity analyses evaluating the influence of varying the treatment identification interval and starting points for measurement of survival also yielded lower, yet insignificant, estimated hazard ratios. Thus, the finding that concurrent use of bevacizumab with platinum-based doublet chemotherapy did not significantly improve overall survival compared to use of platinum-based doublet chemotherapy alone was robust across several analytical models.

4.5 Aim 3: Hospitalizations for Serious Adverse Events

Aim 3 was designed to determine whether the concurrent use of bevacizumab with standard platinum-based doublet chemotherapy is associated with an increase in hospitalization for severe treatment-related adverse events in comparison to platinum-based doublet chemotherapy alone. Hospitalization for each severe adverse event was defined as the presence of an inpatient (MEDPAR) claim with at least one of the corresponding ICD-9 or CPT codes listed in Appendix A during the specified evaluation period.

Two distinct time windows were used to perform separate evaluations of hospitalizations: 1) a 6-month window starting from the first day of treatment; and 2) the duration between the first day and last day of the initial treatment regimen plus 30 days or the day a second-line treatment was initiated, whichever occurred first. Analysis of hospitalizations for severe adverse events over the 6-month window was performed through estimation of the odds of hospitalization for an adverse event among patients who received bevacizumab concurrent with platinum-based doublet chemotherapy relative to those patients who received platinum-based doublet chemotherapy only. Since the duration of first-line treatment varied across patients, analysis of hospitalizations for severe adverse events using the treatment duration window was performed through the estimation of the hazard of hospitalization for an adverse event among patients who received bevacizumab concurrent with platinum-based doublet chemotherapy relative to those patients who received platinum-based doublet chemotherapy only.

Separate analyses were done to evaluate the hazard of hospitalization for each of the severe adverse events of interest, including arterial thromboembolic events, gastrointestinal perforation, neutropenia, and severe hemorrhage as well as a composite measure of hospitalization for any of the aforementioned severe adverse events. Furthermore, additional analyses of hospitalization for severe treatment-related adverse events were performed for those patients who received first-line treatment with a platinum-taxane doublet regimen in particular. Finally, a sensitivity analysis was also

performed to assess the association between the use of bevacizumab and the hazard of hospitalization for severe treatment-related adverse events among patients who specifically received first-line treatment with carboplatin-paclitaxel chemotherapy.

4.5.1 Hospitalization within 180 days from the start of treatment

4.5.1.1 Bivariate analysis of bevacizumab and hospitalization for severe adverse events

The cumulative incidence of hospitalization for severe adverse events within 180 days from the start of treatment is shown in Table 4.14 for patients who received any platinum doublet and in Table 4.15 for patients who received a platinum-taxane regimen. The incidence of hospitalization for severe adverse events was similar between the larger cohort of patients who received any platinum-based doublet chemotherapy and the cohort of patients who received platinum-taxane regimens specifically. Among patients treated with any platinum-based doublet chemotherapy, those who received bevacizumab had lower incidence of arterial thromboembolic events (1.8% vs. 2.8%) but higher incidence of gastrointestinal perforation (2.3% vs. 1.1%) and neutropenia (10.1% vs. 8.6%) compared to patients who did not receive bevacizumab. However, the receipt of bevacizumab was only significantly associated with increased odds of hospitalization for gastrointestinal perforation (any platinum-based doublet: OR 2.24, 95% CI 1.09-4.61; platinum-taxane doublet: OR 2.20, 95% CI 1.01-4.78). The incidence of hospitalization for any adverse event was also higher among patients who received bevacizumab compared to those patients who did not (17.1% vs. 13.8%), but the increased odds was only statistically significant among patients who received a platinum-taxane doublet regimen specifically (OR 1.37, 95% CI 1.01-1.85).

Table 4.14 Cumulative incidence (%) and odds ratios of hospitalization for severe adverse events within 180 days of the start of first-line treatment with any platinum-doublet

	Any platinum doublet		
	Bevacizumab		
Adverse event	No (n = 4360)	Yes (n = 386)	OR (95% CI)
Arterial thromboembolic events	122 (2.8)	7 (1.8)	0.64 (0.30, 1.38)
Gastrointestinal perforation	46 (1.1)	9 (2.3)	2.24 (1.09, 4.61)
Neutropenia	377 (8.6)	39 (10.1)	1.19 (0.84, 1.68)
Severe hemorrhage	196 (4.5)	17 (4.4)	0.98 (0.59, 1.62)
Any adverse event	603 (13.8)	66 (17.1)	1.29 (0.97, 1.70)

Table 4.15 Cumulative incidence (%) and odds ratios of hospitalization for severe adverse events within 180 days of the start of first-line treatment with a platinum-taxane doublet

	Platinum-taxane doublet		
	Bevacizumab		
Adverse event	No (n = 3068)	Yes (n = 333)	OR (95% CI)
Arterial thromboembolic events	80 (2.6)	6 (1.8)	0.69 (0.30, 1.58)
Gastrointestinal perforation	34 (1.1)	8 (2.4)	2.20 (1.01, 4.79)
Neutropenia	268 (8.7)	35 (10.5)	1.23 (0.85, 1.78)
Severe hemorrhage	127 (4.1)	14 (4.2)	1.02 (0.58, 1.79)
Any adverse event	417 (13.6)	59 (17.7)	1.37 (1.01, 1.85)

Bivariate associations between predisposing, enabling, and need characteristics with hospitalization for severe adverse events within 180 days from the start of treatment were assessed to inform multivariable regression models. The bivariate analysis results among patients who received any platinum-based doublet chemotherapy are presented in Table 4.16. Tumor histology (Chi-square p-value = 0.003) and brain metastases (p = 0.004) were significantly associated with hospitalization

for arterial thromboembolic events. The presence of brain metastases ($p = 0.033$) was also significantly associated with hospitalization for gastrointestinal perforation, as was the absence of radiation therapy ($p = 0.049$), NCI Charlson Comorbidity score ($p = 0.037$) and year of diagnosis ($p = 0.017$). Hospitalization for neutropenia was associated with the receipt of radiation treatment ($p = 0.007$) and residence in a non-metropolitan area at the time of diagnosis ($p =0.006$) whereas female sex ($p = 0.032$), race ($p = 0.029$), education ($p = 0.039$), SEER region ($p = 0.26$), greater comorbidity ($p < 0.001$), and presence of hemoptysis ($p = 0.045$) were associated with hospitalization for severe hemorrhage. Female sex ($p = 0.032$), SEER region ($p = 0.013$), and greater comorbidity ($p < 0.001$) were all associated with hospitalization for any severe adverse event.

Among patients who received platinum-taxane doublet chemotherapy specifically (Table 4.17), tumor histology ($p = 0.005$) and greater comorbidity ($p = 0.027$) were significantly associated with hospitalization for arterial thromboembolic events. Greater comorbidity ($p = 0.008$) was also associated with hospitalization for gastrointestinal perforation as was year of diagnosis ($p = 0.015$). No predisposing, enabling, or need characteristics were statistically significantly associated with hospitalization for neutropenia whereas female sex ($p = 0.021$) and greater comorbidity ($p < 0.001$) were both associated with hospitalization for severe hemorrhage and hospitalization for any severe adverse event (female sex, $p = 0.018$; greater comorbidity, $p < 0.001$).

Table 4.16 Bivariate associations between hospitalization for severe adverse events within 180 days of the start of treatment and predisposing, enabling, and need characteristics among patients receiving platinum-based doublet chemotherapy

	ATE		GI Perforation		Neutropenia		Severe Hemorrhage		Any Adverse Event	
Characteristic	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*
Predisposing										
Age at diagnosis		0.916		0.324		0.684		0.103		0.458
66 to 69	31 (2.5)		18 (1.4)		111 (8.8)		44 (3.5)		168 (13.3)	
70 to 79	84 (2.9)		31 (1.1)		256 (8.9)		140 (4.9)		414 (14.4)	
80 and older	14 (2.3)		6 (1.0)		49 (8.1)		29 (4.8)		87 (14.3)	
Sex		0.082		0.971		0.432		0.032		0.032
Female	78 (3.1)		29 (1.2)		228 (9.1)		128 (5.1)		380 (15.1)	
Male	51 (2.3)		26 (1.2)		188 (8.4)		85 (3.8)		289 (12.9)	
Marital Status		0.559		0.572		0.566		0.138		1.000
Not married	46 (2.5)		23 (1.3)		164 (9.1)		71 (3.9)		255 (14.1)	
Married	83 (2.8)		32 (1.1)		252 (8.6)		142 (4.8)		414 (14.1)	
Race		0.226		0.973		0.275		0.029		0.262
White	120 (2.8)		49 (1.2)		362 (8.6)		186 (4.4)		593 (14.1)	
Black	4 (1.4)		3 (1.0)		33 (11.5)		21 (7.3)		48 (16.7)	
Other	5 (2.1)		3 (1.3)		21 (8.8)		6 (2.5)		28 (11.7)	
% 25 years and older in census tract w/ < HS education		0.896		0.911		0.657		0.039		0.466
Lowest quartile	35 (2.6)		15 (1.1)		108 (8.1)		51 (3.8)		173 (12.9)	
Second	33 (2.7)		16 (1.3)		117 (9.4)		51 (4.1)		179 (14.4)	
Third	36 (3.0)		12 (1.0)		108 (9.0)		51 (4.3)		172 (14.4)	
Highest	24 (2.5)		12 (1.3)		83 (8.7)		60 (6.3)		145 (15.1)	

Table 4.16 (Continued)

Enabling						
Median household income (census tract level)		0.856	0.678	0.614	0.503	0.553
Lowest quartile	24 (2.5)	8 (0.8)	93 (9.5)	42 (4.3)	139 (14.2)	
Second	34 (2.9)	15 (1.3)	106 (9.0)	62 (5.3)	180 (15.3)	
Third	31 (2.5)	14 (1.1)	108 (8.8)	49 (4.0)	168 (13.7)	
Highest	40 (2.9)	18 (1.3)	109 (8.0)	60 (4.4)	182 (13.4)	
Population density		0.658	0.222	0.006	0.854	0.050
Urban/rural	17 (2.5)	5 (0.7)	80 (11.6)	30 (4.4)	114 (16.5)	
Metro	112 (2.8)	50 (1.2)	336 (8.3)	183 (4.5)	555 (13.7)	
State buy-in Medicare coverage during year preceding diagnosis		0.092	0.160	0.782	0.420	0.101
No	112 (2.6)	47 (1.1)	378 (8.7)	191 (4.4)	599 (13.8)	
Yes	17 (4.1)	8 (1.9)	38 (9.1)	22 (5.3)	70 (16.8)	
≥ 50% of chemotherapy claims from CCOP-affiliated provider		0.191	0.521	0.499	0.663	0.278
No	102 (2.9)	43 (1.2)	314 (8.9)	160 (4.5)	510 (14.4)	
Yes	22 (2.1)	10 (1.0)	84 (8.2)	44 (4.3)	134 (13.1)	
Received treatment from provider affiliated with a cooperative research group		0.340	0.962	0.345	0.935	0.129
No	60 (3.1)	23 (1.2)	184 (9.4)	112 (5.7)	301 (15.3)	
Yes	63 (2.6)	29 (1.2)	209 (8.5)	89 (3.6)	335 (13.7)	
Year of diagnosis		0.313	0.017	0.637	0.312	0.144
2004-2005	59 (2.5)	32 (1.3)	200 (8.4)	105 (4.4)	321 (13.5)	
2006	32 (2.6)	6 (0.5)	116 (9.3)	49 (3.9)	169 (13.6)	
2007	38 (3.4)	17 (1.5)	100 (8.9)	59 (5.2)	179 (15.9)	

Table 4.16 (continued)

SEER region		0.287	0.257	0.068	0.026	0.013
East	38 (3.4)	16 (1.4)	90 (8.1)	63 (5.7)	162 (14.6)	
Midwest	24 (2.7)	7 (0.8)	98 (11.0)	47 (5.3)	154 (17.2)	
South	40 (2.2)	17 (0.9)	155 (8.6)	72 (4.0)	229 (12.8)	
West	27 (2.8)	15 (1.6)	73 (7.7)	31 (3.3)	124 (13.1)	
Need						
Tumor stage		0.272	0.122	0.649	0.355	0.892
IIIB	32 (2.3)	11 (0.8)	125 (9.1)	56 (4.1)	196 (14.2)	
IV	97 (2.9)	44 (1.3)	291 (8.6)	157 (4.7)	473 (14.1)	
Summary stage		0.963	0.137	0.721	0.254	0.676
Regional	11 (2.7)	2 (0.5)	34 (8.3)	14 (3.4)	55 (13.4)	
Distant	118 (2.7)	53 (1.2)	382 (8.8)	199 (4.6)	614 (14.2)	
Grade		0.805	0.300	0.284	0.669	0.814
Well/Moderately differentiated	12 (2.2)	7 (1.3)	41 (7.6)	21 (3.9)	69 (12.7)	
Poor/Undifferentiated	45 (3.3)	20 (1.4)	120 (8.7)	73 (5.3)	206 (14.9)	
Unknown	72 (2.6)	28 (1.0)	255 (9.0)	119 (4.2)	394 (14.0)	
Tumor histology		0.003	0.687	0.589	0.872	0.991
Adenocarcinoma	65 (2.5)	29 (1.1)	238 (9.0)	121 (4.6)	374 (14.2)	
Large cell	1 (0.4)	2 (0.8)	25 (9.8)	10 (3.9)	36 (14.1)	
Other and NOS	63 (3.4)	24 (1.3)	153 (8.3)	82 (4.4)	259 (14.0)	
NCI Charlson Comorbidity Index		0.064	0.037	0.082	<0.001	<0.001
0	66 (2.3)	25 (0.9)	234 (8.3)	91 (3.2)	351 (12.5)	
1	50 (3.2)	28 (1.8)	142 (9.0)	98 (6.2)	255 (16.1)	
2	11 (4.7)	2 (0.9)	30 (12.8)	22 (9.4)	51 (21.7)	

Table 4.16 (Continued)

Hemoptysis	0.882	0.850	0.644	0.045	0.623	
No	124 (2.7)	53 (1.2)	397 (8.7)	198 (4.4)	639 (14.0)	
Yes	5 (2.6)	2 (1.0)	19 (9.7)	15 (7.7)	30 (15.3)	
Brain metastases	0.004	0.033	0.879	0.375	0.558	
No	84 (2.3)	35 (1.0)	319 (8.8)	168 (4.6)	505 (13.9)	
Yes	45 (4.0)	20 (1.8)	97 (8.7)	45 (4.0)	164 (14.6)	
Radiation therapy received	0.504	0.049	0.007	0.741	0.063	
No	60 (2.5)	35 (1.5)	181 (7.7)	108 (4.6)	312 (13.2)	
Yes	66 (2.9)	20 (0.9)	229 (9.9)	101 (4.4)	349 (15.1)	
Cancer-directed surgery	0.915	0.358	0.230	0.215	0.270	
No	121 (2.7)	53 (1.2)	41 (0.9)	395 (8.9)	203 (4.6)	
Yes	8 (2.6)	2 (0.7)	1 (0.3)	21 (6.9)	10 (3.3)	

Abbreviations: ATE = Arterial thromboembolic event; GI = Gastrointestinal; CCOP = Clinical Community Oncology Program; SEER = Surveillance, Epidemiology, and End Results; NOS = Not otherwise specified; NCI = National Cancer Institute.

Table 4.17 Bivariate associations between hospitalization for severe adverse events within 180 days of the start of treatment and predisposing, enabling, and need characteristics among patients receiving platinum-taxane doublet chemotherapy

	ATE		GI Perforation		Neutropenia		Severe Hemorrhage		Any Adverse Event	
Characteristic	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*
Predisposing										
Age at diagnosis		0.841		0.515		0.316		0.115		0.209
66 to 69	20 (2.3)		12 (1.4)		72 (8.1)		26 (2.9)		113 (12.8)	
70 to 79	56 (2.7)		26 (1.3)		188 (9.1)		96 (4.6)		296 (14.3)	
80 and older	10 (2.2)		4 (0.9)		43 (9.6)		19 (4.3)		67 (15.0)	
Sex		0.063		0.937		0.253		0.021		0.018
Female	54 (3.0)		22 (1.2)		170 (9.4)		88 (4.9)		276 (15.3)	
Male	32 (2.0)		20 (1.3)		133 (8.3)		53 (3.3)		200 (12.5)	
Marital Status		0.393		0.999		0.292		0.507		0.639
Not married	29 (2.2)		16 (1.2)		124 (9.6)		50 (3.9)		186 (14.4)	
Married	57 (2.7)		26 (1.2)		179 (8.5)		91 (4.3)		290 (13.8)	
Race		0.280		0.541		0.647		0.288		0.722
White	81 (2.7)		39 (1.3)		266 (8.8)		122 (4.0)		423 (13.9)	
Black	3 (1.5)		1 (0.5)		21 (10.4)		13 (6.4)		32 (15.8)	
Other	2 (1.3)		2 (1.3)		16 (10.1)		6 (3.8)		21 (13.2)	
% 25 years and older in census tract w/ < HS education		0.924		0.456		0.737		0.068		0.553
Lowest quartile	24 (2.6)		11 (1.2)		75 (8.2)		30 (3.3)		118 (12.9)	
Second	20 (2.2)		14 (1.6)		79 (8.9)		32 (3.6)		122 (13.7)	
Third	24 (2.7)		7 (0.8)		86 (9.7)		38 (4.3)		129 (14.6)	
Highest	17 (2.4)		10 (1.4)		63 (9.0)		41 (5.8)		107 (15.2)	

Table 4.17 (continued)

Enabling						
Median household income (census tract level)		0.932	0.574	0.516	0.778	0.542
Lowest quartile	17 (2.3)	7 (0.9)	69 (9.4)	29 (3.9)	103 (14.0)	
Second	23 (2.7)	14 (1.6)	78 (9.2)	40 (4.7)	129 (15.2)	
Third	21 (2.4)	9 (1.0)	84 (9.5)	37 (4.2)	125 (14.2)	
Highest	25 (2.7)	12 (1.3)	72 (7.7)	35 (3.8)	119 (12.8)	
Population density		0.467	0.500	0.053	0.979	0.136
Urban/rural	11 (2.1)	5 (0.9)	59 (11.2)	22 (4.2)	85 (16.1)	
Metro	75 (2.6)	37 (1.3)	244 (8.5)	119 (4.1)	391 (13.6)	
State buy-in Medicare coverage during year preceding diagnosis		0.975	0.411	0.667	0.111	0.305
No	79 (2.5)	37 (1.2)	280 (9.0)	124 (4.0)	431 (13.8)	
Yes	7 (2.5)	5 (1.8)	23 (8.2)	17 (6.1)	45 (16.1)	
≥ 50% of chemotherapy claims from CCOP-affiliated provider		0.589	0.325	0.663	0.327	0.450
No	18 (2.3)	7 (0.9)	66 (8.4)	28 (3.6)	103 (13.2)	
Yes	66 (2.6)	33 (1.3)	223 (8.9)	109 (4.4)	355 (14.2)	
Received treatment from provider affiliated with a cooperative research group		0.678	0.859	0.489	0.942	0.211
No	39 (2.8)	18 (1.3)	134 (9.5)	60 (4.3)	215 (15.2)	
Yes	44 (2.5)	21 (1.2)	153 (8.8)	75 (4.3)	238 (13.7)	
Year of diagnosis		0.759	0.015	0.754	0.291	0.589
2004-2005	41 (2.4)	24 (1.4)	147 (8.7)	75 (4.4)	231 (13.6)	
2006	22 (2.4)	4 (0.4)	87 (9.5)	30 (3.3)	125 (13.7)	
2007	23 (2.9)	14 (1.8)	69 (8.7)	36 (4.5)	120 (15.1)	

Table 4.17 (Continued)

SEER region		0.896	0.640	0.191	0.241	0.056
East	22 (2.7)	12 (1.5)	69 (8.4)	38 (4.6)	112 (13.6)	
Midwest	17 (2.7)	7 (1.1)	66 (10.6)	33 (5.3)	109 (17.5)	
South	30 (2.3)	13 (1.0)	122 (9.2)	49 (3.7)	173 (13.1)	
West	17 (2.7)	10 (1.6)	46 (7.3)	21 (3.3)	82 (13.0)	
Need						
Tumor stage		0.055	0.104	0.190	0.164	0.086
IIIB	18 (1.8)	8 (0.8)	81 (7.9)	35 (3.4)	127 (12.5)	
IV	68 (2.9)	34 (1.4)	222 (9.3)	106 (4.5)	349 (14.7)	
Summary stage		0.724	0.067	0.115	0.329	0.192
Regional	9 (2.8)	1 (0.3)	21 (6.6)	10 (3.1)	37 (11.6)	
Distant	77 (2.5)	41 (1.3)	282 (9.1)	131 (4.2)	439 (14.2)	
Grade		0.481	0.858	0.430	0.854	0.804
Well/Moderately differentiated	9 (2.2)	5 (1.2)	35 (8.6)	12 (3.0)	52 (12.8)	
Poor/Undifferentiated	32 (3.2)	13 (1.3)	81 (8.2)	52 (5.3)	144 (14.6)	
Unknown	45 (2.2)	24 (1.2)	187 (9.3)	77 (3.8)	280 (13.9)	
Tumor histology		0.005	0.564	0.531	0.686	0.948
Adenocarcinoma	47 (2.4)	23 (1.2)	180 (9.3)	75 (3.9)	269 (13.9)	
Large cell	0 (0.0)	1 (0.6)	17 (9.4)	8 (4.4)	24 (13.3)	
Other and NOS	39 (3.0)	18 (1.4)	106 (8.2)	58 (4.5)	183 (14.2)	
NCI Charlson Comorbidity Index		0.027	0.008	0.141	<0.001	<0.001
0	40 (1.4)	20 (0.7)	174 (6.2)	61 (2.2)	250 (8.9)	
1	36 (2.3)	22 (1.4)	98 (6.2)	66 (4.2)	183 (11.6)	
2	8 (3.4)	0 (0.0)	23 (9.8)	14 (6.0)	34 (14.5)	
Hemoptysis		0.320	0.503	0.542	0.057	0.391
No	84 (2.6)	41 (1.3)	292 (9.0)	130 (4.0)	459 (14.1)	
Yes	2 (1.4)	1 (0.7)	11 (7.5)	11 (7.5)	17 (11.6)	

Table 4.17 (Continued)

Brain metastases		0.074	0.091	0.689	0.994	0.558
No	58 (2.2)	27 (1.0)	227 (8.8)	107 (4.1)	356 (13.8)	
Yes	28 (3.4)	15 (1.8)	76 (9.3)	34 (4.1)	120 (14.6)	
Radiation therapy received		0.202	0.031	0.140	0.723	0.136
No	49 (2.8)	15 (0.9)	167 (9.6)	74 (4.2)	259 (14.8)	
Yes	34 (2.1)	27 (1.7)	130 (8.1)	64 (4.0)	209 (13.0)	
Cancer-directed surgery		0.843	0.230	0.288	0.276	0.054
No	81 (2.5)	41 (1.3)	288 (9.0)	135 (4.2)	455 (14.3)	
Yes	5 (2.3)	1 (0.5)	15 (7.0)	6 (2.8)	21 (9.8)	

Abbreviations: ATE = Arterial thromboembolic event; GI = Gastrointestinal; CCOP = Clinical Community Oncology Program; SEER = Surveillance, Epidemiology, and End Results; NOS = Not otherwise specified; NCI = National Cancer Institute.

4.5.1.2 Multivariate analysis of bevacizumab and hospitalization for severe adverse events

Multivariable logistic regression models were created to assess the relationship between the use of bevacizumab and hospitalization for each severe adverse event within 180 days of treatment start by selecting clinical, sociodemographic, and health system characteristics with statistically significant bivariate associations with the specified adverse event; separate regression models were created for each of the two cohorts (any platinum-based doublet chemotherapy and platinum-taxane doublet chemotherapy), based on the significant bivariate associations between hospitalization for the specified adverse event and the independent variables identified within each cohort. Several multivariable logistic regression models were also created by selecting clinical, sociodemographic, and health system characteristics based on Andersen's Behavioral Model of Health Services Use, including a model of: 1) all predisposing characteristics only; 2) all enabling characteristics only; 3) all need characteristics only; 4) both predisposing and enabling characteristics; and 5) all predisposing, enabling, and need characteristics. However, the results from these regression models do not provide much additional insight into the association between the use of bevacizumab and hospitalization for severe treatment-related adverse events beyond the information obtained from regression models created using only confounding variables (identified through bivariate associations with bevacizumab use and severe adverse events). Therefore the results of the predisposing, enabling, and need logistic regression models were only included as a table in the appendices (Appendix F: Table F-1) and will not be described further in this section.

Results from both the multivariable adjusted logistic regression models (that included only identified confounding variables) and the propensity score-adjusted regression models that evaluated the effect of bevacizumab on hospitalization for severe adverse events among patients who received platinum-based doublet chemotherapy are described in Table 4.18. After adjusting for confounders in a multivariable logistic regression model, patients who received bevacizumab in addition to any platinum-based doublet chemotherapy maintained lower odds of hospitalization for arterial

thromboembolic events compared to patients who received chemotherapy only (OR 0.71, 95% CI 0.33-1.53), though the result was not statistically significant. Conversely, multivariable-adjusted estimates of the odds of hospitalization for gastrointestinal perforation (OR 2.61, 95% CI 1.18-5.80) and any severe adverse event (OR 1.32, 95% CI 1.00-1.75) were significantly higher among patients who received bevacizumab compared to patients who received chemotherapy only. Patients receiving bevacizumab also had higher odds of hospitalization for neutropenia (OR 1.25, 95% CI 0.87-1.80) and severe hemorrhage (OR 1.06, 95% CI 0.64-1.77) compared to patients receiving chemotherapy only, but neither of these results was statistically significant. Results of multivariable-adjusted models estimated among patients who specifically received platinum-taxane chemotherapy were similar to those seen in the larger cohort.

In addition to the multivariable-adjusted survival analyses, Cox proportional hazards models were also constructed using estimated propensity scores. Initially, propensity score analysis was performed to balance measured confounders between patients who received chemotherapy with bevacizumab and patients who received platinum-based chemotherapy only. Multivariate logistic regression models were first used to calculate propensity scores representing the probability that a patient received bevacizumab conditional on all other measured confounders in the model. In each propensity score model, variables that were associated with bevacizumab use and hospitalization for the specified adverse event (true confounders) as well as variables related to hospitalization only were included. Distinct propensity scores were calculated for each adverse event based on the confounders identified in the larger cohort of patients receiving any platinum-based doublet chemotherapy.

Following propensity score estimation, the propensity scores were applied to logistic regressions models to perform two distinct propensity score-adjusted analyses. In the first propensity score-adjusted analysis, discrete logistic regression models were fit using the propensity score as a continuous covariate in the regression model. In the second propensity score-adjusted analysis, propensity score estimates were used to first match exposed patients (receiving bevacizumab) to patients from the unexposed group (receiving chemotherapy only) in a 1:1 ratio using a 5-to-1 digit

greedy-match algorithm. The algorithm allows for the capture of the best possible matches (those pairs matched to the fifth digit of the PS) while also maximizing the number of possible matches by including pairs matched to the fourth, third, second, and first digits of the PS (adequacy of the matches decrease with the number of digits matched on); non-matched individuals are excluded from the derived cohort of matched patients. Application of the 1:1 greedy-match algorithm resulted in a maximum of 386 matched pairs among patients receiving any platinum-based doublet chemotherapy and 333 matched pairs among patients receiving platinum-taxane doublet chemotherapy specifically; fewer patients were matched for gastrointestinal perforation because of missing information for certain covariates that were used to estimate the propensity scores.

Propensity score-adjusted analyses that included the predicted probability of receiving bevacizumab as a linear covariate in each of the logistic regression models estimated similar odds ratios to those observed in the multivariate adjusted models; this is likely due to the similarity between the covariates included in the multivariable-adjusted models and the covariates included in the logistic regression models to estimate the propensity scores for bevacizumab use. Likewise, estimates from propensity score-matched analyses were also similar to estimates from the multivariable-adjusted models although the confidence intervals around the estimates were noticeably larger given the smaller sample sizes in matched analyses. For example, among propensity score-matched patients who received any platinum-based chemotherapy, patients receiving bevacizumab had lower odds of hospitalization for arterial thromboembolic events (OR 0.53, 95% CI 0.21-1.34), but higher odds of hospitalization for neutropenia (OR 1.36, 95% CI 0.81-2.27), severe hemorrhage (OR 1.00, 95% CI 0.50-1.99), and any adverse event (OR 1.33, 95% CI 0.89-1.97) compared to patients who received chemotherapy only; however, no results among propensity score-matched patients were statistically significant. Estimates of the hospitalization for gastrointestinal perforation among patients receiving any platinum-based doublet chemotherapy could not be performed for the propensity-score matched patients due to the occurrence of all hospitalizations within the cohort of patients who received bevacizumab; no hospitalizations for gastrointestinal perforation occurred

among patients who received chemotherapy only. Among propensity score-matched patients receiving platinum-taxane chemotherapy, the estimated odds of hospitalization for gastrointestinal perforation with the use of bevacizumab was nearly three times the odds for chemotherapy only (OR 2.71, 95% CI 0.71, 10.30); still, given the small number of events in each group (8 with bevacizumab; 3 with chemotherapy only), the observed difference was not statistically significant. Additional results among patients receiving platinum-taxane chemotherapy in particular were comparable to those observed among patients receiving any platinum-based doublet chemotherapy.

Table 4.18 Odds ratios of hospitalization for severe adverse events among patients receiving bevacizumab in addition to platinum-based doublet chemotherapy compared to patients who received platinum-based doublet chemotherapy only

Adverse event	Any platinum doublet			Platinum-taxane doublet		
			OR (95% CI)			OR (95% CI)
Arterial thromboembolic events	Sample sizes, n			Sample sizes, n		
Unadjusted	386	4360	0.64 (0.30, 1.38)	333	3068	0.69 (0.30, 1.58)
Multivariable adjusted models:						
Brain metastases, CHF, CVD, histology, and MI	386	4360	0.71 (0.33, 1.53)			
Histology, CHF, CVD, and MI				333	3068	0.72 (0.31, 1.68)
Propensity score-adjusted models[a]						
Covariate adjustment	386	4360	0.71 (0.33, 1.53)	333	3068	0.72 (0.31, 1.66)
Matching	386	386	0.53 (0.21, 1.34)	333	333	0.54 (0.20, 1.47)
Gastrointestinal perforation						
Unadjusted	386	4360	2.24 (1.09, 4.61)	333	3068	2.20 (1.01, 4.79)
Multivariable adjusted models:						
Brain metastases, PVD, receipt of radiation, and year of diagnosis	376	4304	2.61 (1.18, 5.80)			
PVD, receipt of radiation, and year of diagnosis				323	3027	2.41 (1.00, 5.80)
Propensity score-adjusted models[b]						
Covariate adjustment	376	4304	2.67 (1.22, 5.84)	323	3027	2.67 (1.13, 6.30)
Matching[c]	376	376	N/A	323	323	2.71 (0.71, 10.30)

Table 4.18 (Continued)

Neutropenia						
Unadjusted	386	4360	1.19 (0.84, 1.68)	333	3068	1.23 (0.85, 1.78)
Multivariable adjusted models:						
CHF, PVD, population density, and receipt of radiation	386	4360	1.25 (0.87, 1.80)			
CHF, and PVD				333	3068	1.25 (0.86, 1.82)
Propensity score-adjusted models[d]						
Covariate adjustment	386	4360	1.25 (0.87, 1.79)	333	3068	1.25 (0.86, 1.82)
Matching	386	386	1.36 (0.81, 2.27)	333	333	1.23 (0.73, 2.07)
Severe hemorrhage						
Unadjusted	386	4360	0.98 (0.59, 1.63)	333	3068	1.02 (0.58, 1.79)
Multivariable adjusted models:						
COPD, DM, hemoptysis, MI, race, region, history of severe hemorrhage, and sex	386	4360	1.06 (0.64, 1.77)			
COPD, DM, MI, history of severe hemorrhage, and sex				333	3068	1.06 (0.60, 1.87)
Propensity score-adjusted models[e]						
Covariate adjustment	386	4360	1.06 (0.64, 1.77)	333	3068	1.06 (0.60, 1.87)
Matching	386	386	1.00 (0.50, 1.99)	333	333	1.00 (0.47, 2.13)

Table 4.18 (Continued)

Any severe adverse event						
Unadjusted	386	4360	1.29 (0.97, 1.70)	333	3068	1.37 (1.02, 1.85)
Multivariable adjusted models:						
CHF, COPD, CVD, MI, PVD, region and sex	386	4360	1.32 (1.00, 1.75)			
CHF, COPD, CVD, MI, PVD, and sex				333	3068	1.42 (1.05, 1.91)
Propensity score-adjusted models[f]						
Covariate adjustment	386	4360	1.33 (1.00, 1.76)	333	3068	1.42 (1.05, 1.92)
Matching	386	386	1.33 (0.89, 1.97)	333	333	1.38 (0.90, 2.10)

a The propensity of receiving bevacizumab was estimated using a multiple logistic regression model that included brain metastases, CHF, CVD, histology, and MI

b The propensity of receiving bevacizumab was estimated using a multiple logistic regression model that included brain metastases, PVD, receipt of radiation, and year of diagnosis

c Estimates for the propensity score-matched analysis are not available in the larger platinum-based cohort; all hospitalizations for GI perforation occurred among patients who received bevacizumab

d The propensity of receiving bevacizumab was estimated using a multiple logistic regression model that included CHF, PVD, population density, and receipt of radiation

e The propensity of receiving bevacizumab was estimated using a multiple logistic regression model that included COPD, DM, hemoptysis, MI, race, SEER region, history of severe hemorrhage, sex

f The propensity of receiving bevacizumab was estimated using a multiple logistic regression model that included CHF, COPD, CVD, MI, PVD, SEER region, and sex

Abbreviations: OR = Odds ratio; CI = Confidence interval; CHF = Congestive heart failure; CVD = Cerebrovascular disease; MI = Myocardial infarction; PVD = Peripheral vascular disease; N/A = Not available; COPD = Chronic obstructive pulmonary disease; DM = Diabetes mellitus

4.5.2 Hospitalization within first-line treatment duration window

4.5.2.1 Bivariate analysis of bevacizumab and hospitalization for severe adverse events

The cumulative incidence of hospitalization for severe adverse events during the first-line treatment duration window is shown in Table 4.19. The incidence of hospitalization for severe adverse events was similar between the larger cohort of patients who received any platinum-based doublet chemotherapy and the cohort of patients who received platinum-taxane regimens specifically. Among patients treated with any platinum-based doublet chemotherapy, those who received bevacizumab had higher incidence of arterial thromboembolic event (1.8% vs. 1.5%), gastrointestinal perforation (1.8% vs. 0.8%), neutropenia (7.8% vs. 6.9%), and severe hemorrhage (3.9% vs. 2.9%) compared to patients who did not receive bevacizumab. However, the differences in the incidence of hospitalization for these events were not statistically significant. Still, the incidence of hospitalization for any adverse event was more than 4% higher among patients who received bevacizumab compared to those patients who did not (14.0% vs. 9.8%), a finding that was statistically significant among patients who received any platinum-based doublet chemotherapy (log-rank p-value = 0.003) and among patients who received platinum-taxane chemotherapy specifically (log-rank p-value = 0.002).

Table 4.19 Cumulative incidence (%) of hospitalization for severe adverse events during the first-line treatment window

	Any platinum doublet			Platinum-taxane doublet		
	Bevacizumab			Bevacizumab		
Adverse event	No (n = 4360)	Yes (n = 386)	log-rank p-value	No (n = 3068)	Yes (n = 333)	log-rank p-value
ATE	64 (1.5)	7 (1.8)	0.534	37 (1.2)	6 (1.8)	0.362
GI perforation	34 (0.8)	7 (1.8)	0.107	27 (0.9)	6 (1.8)	0.221
Neutropenia	300 (6.9)	30 (7.8)	0.179	218 (7.1)	28 (8.4)	0.109
Severe hemorrhage	127 (2.9)	15 (3.9)	0.142	78 (2.5)	14 (4.2)	0.056
Any adverse event	429 (9.8)	54 (14.0)	0.003	304 (9.9)	50 (15.0)	0.002

Abbreviations: ATE = Arterial thromboembolic event; GI = Gastrointestinal.

Bivariate associations between predisposing, enabling, and need characteristics with the hazard hospitalization for severe adverse events during first-line treatment duration were assessed to inform multivariable regression models. Among patients who received any platinum-based doublet chemotherapy (Table 4.20), distant stage disease and receipt of chemotherapy from a provider not affiliated with a cooperative research group were significantly associated with the hazard of hospitalization for arterial thromboembolic events (log-rank p-value = 0.017) and gastrointestinal perforation (p-value = 0.007), respectively. Residence in a non-metropolitan area (p = 0.007) and year of diagnosis (p = 0.049) were significantly associated with the hazard of hospitalization for neutropenia, and year of diagnosis (p = 0.022) and stage IV disease (p = 0.023) were significantly associated with the hazard of hospitalization for severe hemorrhage. Distant stage disease (p = 0.002), year of diagnosis (p = 0.014), stage IV disease (p = 0.008), receipt of radiation treatment (p = 0.039), and non-receipt of cancer-directed surgery (p = 0.012) were all significantly associated with hospitalization for any severe adverse event.

Among patients who received platinum-taxane doublet chemotherapy specifically (Table 4.21), no characteristics were significantly associated with the hazard of hospitalization for arterial thromboembolic events. Receipt of chemotherapy treatment from a provider not affiliated with a cooperative research group (log-rank p-value = 0.001) was significantly associated with the hazard of hospitalization for gastrointestinal perforation whereas residence in a non-metropolitan area (p = 0.022), stage IV disease (p = 0.037), and distant stage disease (p = 0.041) were significantly associated with the hazard of hospitalization for neutropenia. Hemoptysis (p = 0.015) was significantly associated with the hazard of hospitalization for severe hemorrhage while year of diagnosis (p = 0.019), receipt of treatment from a provider not affiliated with CCOP (0.022), stage IV disease (p = 0.003), distant stage disease (p = 0.006), and no cancer-directed surgery (p = 0.034) were significantly associated with the hazard of hospitalization for any severe adverse events.

Table 4.20 Bivariate associations between the hazard rate of hospitalization for severe adverse events during first-line treatment and predisposing, enabling, and need characteristics among patients receiving platinum-based doublet chemotherapy.

	ATE		GI Perforation		Neutropenia		Severe Hemorrhage		Any Adverse Event	
Characteristic	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*
Predisposing										
Age at diagnosis		0.149		0.327		0.219		0.199		0.389
66 to 69	18 (1.4)		13 (1.0)		84 (6.7)		29 (2.3)		116 (9.2)	
70 to 79	48 (1.7)		23 (0.8)		203 (7.1)		92 (3.2)		301 (10.5)	
80 and older	5 (0.8)		5 (0.8)		43 (7.1)		21 (3.5)		66 (10.9)	
Sex		0.808		0.597		0.488		0.232		0.419
Female	31 (1.4)		18 (0.8)		152 (6.8)		56 (2.5)		211 (9.5)	
Male	40 (1.6)		23 (0.9)		178 (7.1)		86 (3.4)		272 (10.8)	
Marital Status		0.671		0.087		0.582		0.516		0.856
Not married	25 (1.4)		18 (1.0)		124 (6.9)		47 (2.6)		178 (9.8)	
Married	46 (1.6)		23 (0.8)		206 (7.0)		95 (3.2)		305 (10.4)	
Race		0.443		0.592		0.891		0.115		0.158
White	64 (37.0)		37 (0.9)		287 (6.8)		130 (3.1)		435 (10.3)	
Black	4 (1.4)		1 (0.3)		28 (9.7)		10 (3.5)		31 (10.8)	
Other	3 (1.3)		3 (1.3)		15 (6.3)		2 (0.8)		17 (7.1)	
% 25 years and older in census tract w/ < HS education		0.940		0.847		0.517		0.747		0.945
Lowest quartile	20 (1.5)		12 (0.9)		76 (5.7)		36 (2.7)		123 (9.2)	
Second	16 (1.3)		9 (0.7)		95 (7.7)		31 (2.5)		126 (10.2)	
Third	20 (1.7)		11 (0.9)		91 (7.6)		35 (2.9)		129 (10.8)	
Highest	15 (1.6)		9 (0.9)		68 (7.1)		40 (4.2)		105 (10.9)	

Table 4.20 (Continued)

Enabling										
Median household income (census tract level)		0.991		0.384		0.312		0.324		0.971
Lowest quartile	16 (1.6)		6 (0.6)		77 (7.9)		28 (2.9)		102 (10.5)	
Second	18 (1.5)		11 (0.9)		81 (6.9)		45 (3.8)		129 (10.9)	
Third	18 (1.5)		12 (1.0)		87 (7.1)		28 (2.3)		123 (10.0)	
Highest	19 (1.4)		12 (0.9)		85 (6.2)		41 (3.0)		129 (9.5)	
Population density		0.591		0.677		0.007		0.946		0.106
Urban/rural	9 (1.3)		3 (0.4)		70 (10.2)		22 (3.2)		89 (12.9)	
Metro	62 (1.5)		38 (0.9)		260 (6.4)		120 (3.0)		394 (9.7)	
State buy-in Medicare coverage during year preceding diagnosis		0.863		0.895		0.447		0.348		0.067
No	63 (1.5)		35 (0.8)		300 (6.9)		130 (3.0)		440 (10.2)	
Yes	8 (1.9)		6 (1.4)		30 (7.2)		12 (2.9)		43 (10.3)	
≥ 50% of chemotherapy claims from CCOP-affiliated provider		0.396		0.113		0.108		0.329		0.092
No	56 (1.6)		28 (0.8)		246 (6.9)		109 (3.1)		366 (10.3)	
Yes	12 (1.2)		10 (1.0)		66 (6.4)		27 (2.6)		95 (9.3)	
Received treatment from provider affiliated with a cooperative research group		0.534		0.007		0.876		0.579		0.151
No	30 (1.5)		21 (1.1)		145 (7.4)		62 (3.2)		218 (11.1)	
Yes	38 (1.6)		16 (0.7)		163 (6.7)		73 (3.0)		238 (9.7)	
Year of diagnosis		0.595		0.341		0.049		0.022		0.014
2004-2005	34 (1.4)		21 (0.9)		147 (6.2)		55 (2.3)		215 (9.0)	
2006	16 (1.3)		4 (0.3)		104 (8.4)		42 (3.4)		135 (10.9)	
2007	21 (1.9)		16 (1.4)		79 (7.0)		45 (4.0)		133 (11.8)	

Table 4.20 (Continued)

SEER region		0.256	0.515	0.397	0.604	0.050
East	19 (1.7)	11 (1.0)	70 (6.3)	37 (3.3)	111 (10.0)	
Midwest	17 (1.9)	6 (0.7)	81 (9.1)	34 (3.8)	118 (13.2)	
South	22 (1.2)	14 (0.8)	126 (7.0)	50 (2.8)	173 (9.6)	
West	13 (1.4)	10 (1.1)	53 (5.6)	21 (2.2)	81 (8.5)	
Need						
Tumor stage		0.051	0.219	0.056	0.023	0.008
IIIB	17 (1.2)	9 (0.7)	101 (7.3)	38 (2.8)	140 (10.1)	
IV	54 (1.6)	32 (1.0)	229 (6.8)	104 (3.1)	343 (10.2)	
Summary stage		0.017	0.488	0.028	0.174	0.002
Regional	4 (1.0)	2 (0.5)	27 (6.6)	12 (2.9)	37 (9.0)	
Distant	67 (1.5)	39 (0.9)	303 (7.0)	130 (3.0)	446 (10.3)	
Grade		0.177	0.810	0.641	0.736	0.217
Well/Moderately differentiated	6 (1.1)	5 (0.9)	33 (6.1)	13 (2.4)	47 (8.7)	
Poor/Undifferentiated	21 (1.5)	13 (0.9)	96 (6.9)	44 (3.2)	144 (10.4)	
Unknown	44 (1.6)	23 (0.8)	201 (7.1)	85 (3.0)	292 (10.4)	
Tumor histology		0.490	0.158	0.589	0.076	0.468
Adenocarcinoma	34 (1.3)	20 (0.8)	189 (7.2)	74 (2.8)	264 (10.0)	
Large cell	2 (0.8)	1 (0.4)	22 (8.6)	7 (2.7)	28 (10.9)	
Other and NOS	35 (1.9)	20 (1.1)	119 (6.4)	61 (3.3)	191 (10.3)	
NCI Charlson Comorbidity Index		0.270	0.099	0.133	0.186	0.478
0	38 (1.4)	20 (0.7)	178 (6.3)	61 (2.2)	249 (8.8)	
1	24 (1.5)	21 (1.3)	118 (7.5)	64 (4.1)	186 (11.8)	
2	8 (3.4)	0 (0.0)	25 (10.6)	16 (6.8)	38 (16.2)	

Table 4.20 (Continued)

Hemoptysis		0.266	0.847	0.678	0.195	0.899
No	66 (1.5)	38 (0.8)	313 (6.9)	133 (2.9)	462 (10.2)	
Yes	5 (2.6)	3 (1.5)	17 (8.7)	9 (4.6)	21 (10.7)	
Brain metastases		0.410	0.139	0.628	0.156	0.253
No	50 (1.4)	27 (0.7)	249 (6.9)	114 (3.1)	369 (10.2)	
Yes	21 (1.9)	14 (1.2)	81 (7.2)	28 (2.5)	114 (10.2)	
Radiation therapy received		0.722	0.112	0.544	0.384	0.039
No	36 (1.5)	25 (1.1)	143 (6.0)	69 (2.9)	226 (9.6)	
Yes	34 (1.5)	16 (0.7)	183 (7.9)	70 (3.0)	253 (10.9)	
Cancer-directed surgery		0.177	0.045	0.140	0.156	0.012
No	67 (1.5)	40 (0.9)	312 (7.0)	136 (3.1)	460 (10.4)	
Yes	4 (1.3)	1 (0.3)	18 (5.9)	6 (2.0)	23 (7.5)	

Abbreviations: ATE = Arterial thromboembolic event; GI = Gastrointestinal; CCOP = Clinical Community Oncology Program; SEER = Surveillance, Epidemiology, and End Results; NOS = Not otherwise specified; NCI = National Cancer Institute.

Table 4.21 Bivariate associations between the hazard of hospitalization for severe adverse events during first-line treatment and predisposing, enabling, and need characteristics among patients receiving platinum-taxane doublet chemotherapy

	ATE		GI Perforation		Neutropenia		Severe Hemorrhage		Any Adverse Event	
Characteristic	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*
Predisposing										
Age at diagnosis		0.283		0.600		0.074		0.248		0.051
66 to 69	11 (1.2)		9 (1.0)		54 (6.1)		17 (1.9)		78 (8.8)	
70 to 79	29 (1.4)		20 (1.0)		154 (7.4)		62 (3.0)		223 (10.8)	
80 and older	3 (0.7)		4 (0.9)		38 (8.5)		13 (2.9)		53 (11.9)	
Sex		0.989		0.553		0.889		0.154		0.480
Female	19 (1.2)		14 (0.9)		110 (6.9)		33 (2.1)		152 (9.5)	
Male	24 (1.3)		19 (1.1)		136 (7.5)		59 (3.3)		202 (11.2)	
Marital Status		0.273		0.182		0.442		0.710		0.240
Not married	17 (1.3)		12 (0.9)		96 (7.4)		32 (2.5)		135 (10.4)	
Married	26 (1.2)		21 (1.0)		150 (7.1)		60 (2.9)		219 (10.4)	
Race		0.290		0.920		0.970		0.371		0.262
White	39 (30.0)		30 (1.0)		215 (7.1)		84 (2.8)		318 (10.5)	
Black	3 (1.5)		1 (0.5)		19 (9.4)		6 (3.0)		23 (11.4)	
Other	1 (0.6)		2 (1.3)		12 (7.5)		2 (1.3)		13 (8.2)	
% 25 years and older in census tract w/ < HS education		0.685		0.390		0.746		0.952		0.899
Lowest quartile	12 (1.3)		10 (1.1)		54 (5.9)		20 (2.2)		84 (9.2)	
Second	7 (0.8)		9 (1.0)		68 (7.6)		20 (2.2)		91 (10.2)	
Third	15 (1.7)		6 (0.7)		72 (8.1)		28 (3.2)		101 (11.4)	
Highest	9 (1.3)		8 (1.1)		52 (7.4)		24 (3.4)		78 (11.1)	

Table 4.21 (Continued)

Enabling										
Median household income (census tract level)		0.521		0.856		0.574		0.689		0.757
Lowest quartile	11 (1.5)		5 (0.7)		58 (7.9)		18 (2.4)		77 (10.4)	
Second	11 (1.3)		11 (1.3)		62 (7.3)		30 (3.5)		98 (11.5)	
Third	13 (1.5)		8 (0.9)		70 (7.9)		21 (2.4)		96 (10.9)	
Highest	8 (0.9)		9 (1.0)		56 (6.0)		23 (2.5)		83 (8.9)	
Population density		0.321		0.556		0.022		0.607		0.175
Urban/rural	4 (0.8)		3 (0.6)		53 (10.0)		16 (3.0)		67 (12.7)	
Metro	39 (1.4)		30 (1.0)		193 (6.7)		76 (2.6)		287 (10.0)	
State buy-in Medicare coverage during year preceding diagnosis		0.321		0.364		0.079		0.618		0.097
No	41 (1.3)		29 (0.9)		227 (7.3)		84 (2.7)		325 (10.4)	
Yes	2 (0.7)		4 (1.4)		19 (6.8)		8 (2.9)		29 (10.4)	
≥ 50% of chemotherapy claims from CCOP-affiliated provider		0.506		0.756		0.055		0.112		0.022
No	32 (1.3)		23 (0.9)		179 (7.2)		73 (2.9)		263 (10.5)	
Yes	9 (1.2)		7 (0.9)		53 (6.8)		16 (2.0)		73 (9.3)	
Received treatment from provider affiliated with a cooperative research group		0.184		0.001		0.813		0.563		0.142
No	15 (1.1)		16 (1.1)		110 (7.8)		42 (3.0)		161 (11.4)	
Yes	26 (1.5)		13 (0.7)		120 (6.9)		47 (2.7)		172 (9.9)	
Year of diagnosis		0.719		0.060		0.071		0.121		0.019
2004-2005	23 (1.4)		15 (0.9)		111 (6.6)		38 (2.2)		159 (9.4)	
2006	9 (1.0)		3 (0.3)		79 (8.6)		27 (3.0)		102 (11.2)	
2007	11 (1.4)		15 (1.9)		56 (7.1)		27 (3.4)		93 (11.7)	

Table 4.21 (Continued)

SEER region		0.475	0.519	0.489	0.733	0.261
East	8 (1.0)	7 (0.9)	53 (6.4)	20 (2.4)	75 (9.1)	
Midwest	12 (1.9)	6 (1.0)	59 (9.5)	25 (4.0)	88 (14.1)	
South	16 (1.2)	12 (0.9)	99 (7.5)	32 (2.4)	133 (10.1)	
West	7 (1.1)	8 (1.3)	35 (5.5)	15 (2.4)	58 (9.2)	
Need						
Tumor stage		0.059	0.474	0.037	0.053	0.003
IIIB	8 (0.8)	8 (0.8)	67 (6.6)	24 (2.4)	93 (9.1)	
IV	35 (1.5)	25 (1.0)	179 (7.5)	68 (2.9)	261 (11.0)	
Summary stage		0.137	0.807	0.041	0.382	0.006
Regional	3 (0.9)	2 (0.6)	18 (5.7)	8 (2.5)	26 (8.2)	
Distant	40 (1.3)	31 (1.0)	228 (7.4)	84 (2.7)	328 (10.6)	
Grade		0.471	0.575	0.865	0.910	0.541
Well/Moderately differentiated	5 (1.2)	5 (1.2)	31 (7.6)	9 (2.2)	42 (10.3)	
Poor/Undifferentiated	13 (1.3)	9 (0.9)	64 (6.5)	29 (2.9)	101 (10.3)	
Unknown	25 (1.2)	19 (0.9)	151 (7.5)	54 (2.7)	211 (10.5)	
Tumor histology		0.887	0.191	0.387	0.052	0.953
Adenocarcinoma	24 (1.2)	18 (0.9)	147 (7.6)	47 (2.4)	201 (10.4)	
Large cell	1 (0.6)	1 (0.6)	15 (8.3)	5 (2.8)	18 (10.0)	
Other and NOS	18 (1.4)	14 (1.1)	84 (6.5)	40 (3.1)	135 (10.5)	
NCI Charlson Comorbidity Index		0.473	0.201	0.491	0.639	0.741
0	24 (1.2)	16 (0.8)	136 (6.7)	42 (2.1)	186 (9.2)	
1	13 (1.2)	17 (1.5)	82 (7.3)	39 (3.5)	132 (11.8)	
2	5 (2.9)	0 (0.0)	20 (11.6)	11 (6.4)	28 (16.2)	

Table 4.21 (Continued)

Hemoptysis		0.791	0.759	0.712	0.015	0.702
No	41 (1.3)	31 (1.0)	235 (7.2)	84 (2.6)	340 (10.4)	
Yes	2 (1.4)	2 (1.4)	111 (76.0)	8 (5.5)	14 (9.6)	
Brain metastases		0.143	0.244	0.840	0.221	0.173
No	32 (1.2)	22 (0.9)	182 (7.1)	73 (2.8)	269 (10.4)	
Yes	11 (1.3)	11 (1.3)	64 (7.8)	19 (2.3)	85 (10.4)	
Radiation therapy received		0.961	0.165	0.890	0.175	0.210
No	20 (1.2)	20 (1.2)	104 (6.5)	40 (2.5)	159 (9.9)	
Yes	22 (1.3)	13 (0.7)	138 (7.9)	50 (2.9)	191 (10.9)	
Cancer-directed surgery		0.284	0.053	0.236	0.544	0.034
No	40 (1.3)	32 (1.0)	234 (7.3)	89 (2.8)	339 (10.6)	
Yes	3 (1.4)	1 (0.5)	12 (5.6)	3 (1.4)	15 (7.0)	

Abbreviations: ATE = Arterial thromboembolic event; GI = Gastrointestinal; CCOP = Clinical Community Oncology Program; SEER = Surveillance, Epidemiology, and End Results; NOS = Not otherwise specified; NCI = National Cancer Institute.

4.5.2.2 Multivariate analysis of bevacizumab and hospitalization for severe adverse events

Multivariable proportional hazards models were created to assess the relationship between the use of bevacizumab and hospitalization for each severe adverse event during the duration of first-line treatment by selecting clinical, sociodemographic, and health system characteristics with statistically significant bivariate associations with the specified adverse event. In addition, for each adverse event, separate proportional hazards models were created for the two cohorts (any platinum-based doublet chemotherapy and platinum-taxane doublet chemotherapy), based on the significant bivariate associations between hospitalization for the specified adverse event and the independent variables identified within each cohort. Several multivariable proportional hazards models were also created by selecting clinical, sociodemographic, and health system characteristics based on Andersen's Behavioral Model of Health Services Use, including a model of: 1) all predisposing characteristics only; 2) all enabling characteristics only; 3) all need characteristics only; 4) both predisposing and enabling characteristics; and 5) all predisposing, enabling, and need characteristics. However, results from these hazards models do not provide much additional insight into the association between the use of bevacizumab and hospitalization for severe adverse events beyond that obtained from hazards models only confounding variables (identified through bivariate associations with bevacizumab use and severe adverse events). Therefore the results of the predisposing, enabling, and need logistic regression models were only included as a table in the appendices (Appendix F; Table F-2) and will not be described further in this section.

Results from multivariable adjusted proportional hazards models (that included only identified confounding variables) and the propensity score-adjusted hazards models that evaluated the effect of bevacizumab on hospitalization for severe adverse events during the duration of first-line treatment among patients who received platinum-based doublet chemotherapy are described in Table 4.22. After adjusting for confounders in multivariable logistic regression models, patients who received bevacizumab in addition to any platinum-based doublet chemotherapy maintained higher

estimated hazard rates of hospitalization for all adverse events compared to patients who received chemotherapy only: arterial thromboembolic events (HR 1.13, 95% CI 0.47-2.31); gastrointestinal perforation (HR 1.67, 95% CI 0.63, 3.74); neutropenia (HR 1.17, 95% CI 0.77, 1.72); severe hemorrhage (HR 1.20, 95% CI 0.66, 2.04); and any adverse event (HR 1.31, 95% CI 0.94, 1.79). However, none of the results were statistically significant. Overall, results from multivariable-adjusted models among patients who specifically received platinum-taxane chemotherapy were similar to those seen in the larger cohort; point estimates of the hazard ratio were slightly higher in the platinum-taxane cohort for each of the adverse events, further suggesting that patients who received bevacizumab had higher rates of hospitalization than patients who received chemotherapy only, but these results were not statistically significant.

In addition to the multivariable-adjusted analyses, Cox proportional hazards models were also constructed using estimated propensity scores. Initially, propensity score analysis was performed to balance measured confounders between patients who received chemotherapy with bevacizumab and patients who received platinum-based chemotherapy only. Multivariate logistic regression models were first used to calculate propensity scores representing the probability that a patient received bevacizumab conditional on all other measured confounders in the model. In each propensity score model, variables that were associated with bevacizumab use and hospitalization for the specified adverse event (true confounders) as well as variables related to hospitalization only were included. Distinct propensity scores were calculated for each adverse event based on the confounders identified in the larger cohort of patients receiving any platinum-based doublet chemotherapy.

Following propensity score estimation, the propensity scores were applied to Cox proportional hazards models to perform two distinct propensity score-adjusted analyses. In the first propensity score-adjusted analysis, discrete Cox models were fit using the propensity score as a continuous covariate in the model. In the second propensity score-adjusted analysis, propensity score estimates were used to first match exposed patients (receiving bevacizumab) to patients from the unexposed group (receiving chemotherapy only) in a 1:1 ratio using a 5-to-1 digit greedy-match

algorithm. The algorithm allows for the capture of the best possible matches (those pairs matched to the fifth digit of the PS) while also maximizing the number of possible matches by including pairs matched to the fourth, third, second, and first digits of the PS (adequacy of the matches decrease with the number of digits matched on); non-matched individuals are excluded from the derived cohort of matched patients. Application of the 1:1 greedy-match algorithm resulted in a maximum of 386 matched pairs among patients receiving any platinum-based doublet chemotherapy and 333 matched pairs among patients receiving platinum-taxane doublet chemotherapy specifically; fewer patients were matched in the estimates of hospitalization for gastrointestinal perforation and any severe adverse event because of missing information for certain covariates used to estimate the propensity scores within these analyses.

Propensity score-adjusted analyses that included the predicted probability of receiving bevacizumab as a linear covariate in each of the Cox proportional hazards models estimated similar hazards ratios to those observed in the multivariate-adjusted models; this is likely due to the similarity between the covariates included in the multivariable-adjusted models and the covariates included in the logistic regression models to estimate the propensity scores for bevacizumab use. Estimates from propensity score-matched analyses differed somewhat from multivariable-adjusted results although no findings were statistically significant and the confidence intervals around the estimates from propensity score-matched analyses were noticeably larger given the smaller sample sizes. For example, among propensity score-matched patients who received any platinum-based chemotherapy, patients receiving bevacizumab retained higher hazards of hospitalization for arterial thromboembolic events (HR 1.03, 95% CI 0.35-3.02), gastrointestinal perforation (HR 1.86, 95% CI 0.43, 12.69), neutropenia (HR 1.27, 95% CI 0.76-2.13), severe hemorrhage (HR 1.00, 95% CI 0.49-2.07), and any adverse event (HR 1.30, 95% CI 0.84-2.03) compared to patients who received chemotherapy only. Among propensity score-matched patients receiving platinum-taxane chemotherapy, the estimated hazards of hospitalization for severe adverse events were generally similar to those seen in the larger

cohort although the hazard ratio estimates and width of the 95% confidence intervals of hospitalization for arterial thromboembolic events (HR 2.35, 95% CI 0.61,11.21) and gastrointestinal perforation (HR1.06 , 95% CI 0.26, 5.20) were noticeably different; still, no findings within the platinum-taxane cohort were statistically significant.

Table 4.22 Hazards ratios of hospitalization for severe adverse events among patients receiving bevacizumab in addition to platinum-based doublet chemotherapy compared to patients who received platinum-based doublet chemotherapy only

			Any platinum doublet			Platinum-taxane doublet
Adverse event	Sample sizes, n		**HR (95% CI)**	Sample sizes, n		**HR (95% CI)**
Arterial thromboembolic events						
Unadjusted	386	4360	1.28 (0.53, 2.61)	333	3068	1.49 (0.57, 3.29)
Multivariable adjusted models						
Summary stage	386	4360	1.13 (0.47, 2.31)	333	3068	1.35 (0.51, 3.00)
Propensity score-adjusted models[a]						
Covariate adjustment	386	4360	1.13 (0.47, 2.31)	333	3068	1.35 (0.51, 3.00)
Matching	386	386	1.03 (0.35, 3.02)	333	333	2.35 (0.61, 11.21)
Gastrointestinal perforation						
Unadjusted	386	4360	1.93 (0.79, 4.10)	333	3068	1.73 (0.64, 3.92)
Multivariable adjusted models						
Cooperative research group-affiliated provider	366	4044	1.67 (0.63, 3.74)	319	2834	1.81 (0.61, 4.45)
Propensity score-adjusted models[b]						
Covariate adjustment	366	4044	1.67 (0.63, 3.74)	319	2834	1.81 (0.61, 4.45)
Matching	366	366	1.86 (0.43, 12.69)	319	319	1.06 (0.26, 5.20)
Neutropenia						
Unadjusted	386	4360	1.30 (0.83, 1.85)	333	3068	1.38 (0.91, 2.01)
Multivariable adjusted models						
Population density, year of diagnosis, AJCC stage	386	4360	1.17 (0.77, 1.72)	333	3068	1.23 (0.79, 1.85)
Propensity score-adjusted models[c]						
Covariate adjustment	386	4360	1.15 (0.76, 1.68)	333	3068	1.21 (0.78, 1.81)
Matching	386	386	1.27 (0.76, 2.13)	333	333	1.19 (0.68, 2.10)

Table 4.22 (Continued)

Severe hemorrhage						
Unadjusted	386	4360	1.49 (0.84, 2.46)	333	3068	1.73 (0.94, 2.96)
Multivariable adjusted models						
Year of diagnosis, AJCC stage, histology, hemoptysis at diagnosis	386	4360	1.20 (0.66, 2.04)	333	3068	1.48 (0.76, 2.70)
Propensity score-adjusted models[d]						
Covariate adjustment	386	4360	1.15 (0.63, 1.96)	333	3068	1.41 (0.73, 2.59)
Matching	386	386	1.00 (0.49, 2.07)	333	333	1.20 (0.52, 3.02)
Any severe adverse event						
Unadjusted	386	4360	1.53 (1.14, 2.01)	333	3068	1.62 (1.19, 2.16)
Multivariable adjusted models						
CCOP-affiliated provider, year of diagnosis, AJCC stage, receipt of radiation treatment, cancer-directed surgery	364	4128	1.31 (0.94, 1.79)	315	2901	1.38 (0.97, 1.94)
Propensity score-adjusted models[e]						
Covariate adjustment	364	4128	1.31 (0.93, 1.79)	315	2901	1.37 (0.96, 1.93)
Matching	364	364	1.30 (0.84, 2.03)	315	315	1.21 (0.77, 1.91)

a The propensity of receiving bevacizumab was estimated using a multiple logistic regression model that included summary stage at diagnosis
b The propensity of receiving bevacizumab was estimated using a multiple logistic regression model that included cooperative research group-affiliated provider
c The propensity of receiving bevacizumab was estimated using a multiple logistic regression model that included population density, year of diagnosis, and AJCC stage at diagnosis
d The propensity of receiving bevacizumab was estimated using a multiple logistic regression model that included year of diagnosis, AJCC stage, histology, and hemoptysis at diagnosis
e The propensity of receiving bevacizumab was estimated using a multiple logistic regression model that included CCOP-affiliated provider, year of diagnosis, AJCC stage, receipt of radiation treatment, and cancer-directed surgery
Abbreviations: HR = Hazard ratio; CI = Confidence interval; AJCC = American Joint Committee on Cancer; CCOP = Community Clinical Oncology Program.

4.5.3 Summary of analysis of severe treatment-related adverse events

In multivariable-adjusted analyses, patients receiving bevacizumab had significantly higher odds of hospitalization for gastrointestinal perforation or any severe treatment-related adverse event within 180 days from the start of treatment compared to patients who received chemotherapy alone. However, when patients were matched on their estimated propensity to receive bevacizumab, the increased odds of hospitalization for either gastrointestinal perforation or any severe adverse event among patients receiving bevacizumab was no longer significant. In addition, unadjusted estimates of the hazard of hospitalization for severe treatment-related adverse events during first-line treatment suggested a significant increase in the hazard of hospitalization for any severe adverse event among patients who received bevacizumab in comparison to those who did not. However, after controlling for confounding variables through the use of multivariable-adjusted and propensity score-adjusted models, the increased hazard was no longer statistically significant. An important limitation to note in this analysis is the small number of events identified; a small baseline risk of hospitalization for each of the specified adverse events and the small overall sample size likely hindered the ability of this study to identify a significant difference in hospitalizations between patients receiving bevacizumab and patients receiving chemotherapy alone, particularly if the true effect estimate is not considerably large. Thus, although the general findings in this analysis suggest no significant difference in hospitalization for severe adverse events between patients who received bevacizumab and those who did not, the results should be interpreted with an understanding of this limitation.

CHAPTER FIVE

DISCUSSION

5.1 Utilization of Bevacizumab

The objective of this study was to describe the utilization of bevacizumab in combination with standard platinum-based doublet chemotherapy as first line treatment of older adults with advanced NSCLC and to identify the clinical, sociodemographic, and health system factors associated with its use. Key independent variables of interest included patient age, race, socioeconomic status (as measured through census tract level data on education level and median household income), and receipt of chemotherapy treatment from a provider affiliated with the National Cancer Institute's Community Clinical Oncology Program (CCOP). The analysis started with assessment of the utilization of bevacizumab across a cohort of older patients who received any platinum-based doublet regimen as their initial chemotherapy treatment. A subgroup analysis was also performed to evaluate the use of bevacizumab among older patients who were specifically initiated on a platinum-taxane doublet regimen.

Overall, bevacizumab was not utilized to a large extent among the cohort of Medicare patients with advanced NSCLC treated first line with platinum-based doublet chemotherapy. Less than 10% of the entire cohort received bevacizumab within 8 days from the start of chemotherapy treatment and only 812/4746 (17.1%) of patients received bevacizumab at any point following their NSCLC diagnosis. Similar results were found in the subgroup analysis of patients specifically receiving platinum-taxane regimens with less than 10% receiving bevacizumab within 8 days of treatment start and less than 20% ever receiving bevacizumab. However, it is important to note that the proportion of patients who received bevacizumab significantly increased with increasing year of diagnosis. Less than 2% of patients diagnosed in 2004 or 2005 received bevacizumab within 8 days of

chemotherapy start compared to approximately 12% of patients diagnosed in 2006 and 18% of patients diagnosed in 2007.

A primary reason for the low utilization of bevacizumab overall as well as the trend of increased use observed over time is likely to be the fact that bevacizumab was not approved by the FDA for the treatment of NSCLC until October 2006. Thus, it may be unreasonable to expect frequent use of bevacizumab as a component of initial treatment among patients in the study cohort, particularly given that approximately half of the patients were diagnosed in 2004-2005. Still, the utilization of bevacizumab in this cohort following FDA approval was low (< 25% of patients), suggesting that many oncologists may have been hesitant to adopt the practice of adding bevacizumab to platinum-based doublet chemotherapy in older adults with advanced NSCLC, perhaps because of uncertainty with regard to its safety and/or effectiveness in these patients. Given that approval of bevacizumab for the treatment of advanced NSCLC was largely based on results of the ECOG 4599 trial,[56] a study in which over half of patients were under the age of 65, little clinical evidence was available to most oncologists regarding the use of bevacizumab among older patients until a sub-group analysis of ECOG 4599 patients 70 years and older was presented at the American Society of Clinical Oncology Annual Meeting in mid-2007.[207]

Despite the finding of low overall utilization among Medicare patients with advanced NSCLC, chronological age did not appear to be a significant determinant of bevacizumab use. Approximately 9% of patients aged 66-69 and 8% of patients aged 70 and older treated with any platinum-based doublet chemotherapy also received bevacizumab during initial treatment. This finding was contrary to the hypothesis that older patients (i.e., those aged 70 and older) would be less likely than younger patients to receive bevacizumab in addition to first-line chemotherapy. Although a possible explanation for this finding might be that patients 70 years and older were as healthy or healthier in general as compared to younger patients and therefore potentially equally fit as candidates for the receipt of bevacizumab, patients aged 70 and older were significantly more likely to have an NCI Charlson comorbidity score greater than 0 as compared to patients 66-69 years of age (41.1% vs.

35.7%). In addition, among the 9 patients with an NCI Charlson comorbidity score of 2 who received bevacizumab, all of them were 70 years of age or older. Thus, a more reasonable explanation for the lack of difference in utilization of bevacizumab across age groups may be that oncologists had an expectation for a greater level of comorbidity in older adults and were willing to make treatment decisions primarily based on whether or not they felt patients would benefit from the addition of bevacizumab, regardless of age. Still, without additional information such as patient preferences or the determinants of physician treatment decisions, the reason the use of bevacizumab did not vary significantly across age groups in this study can only be speculated.

The utilization of bevacizumab also did not differ significantly across racial groups, a finding contrary to the hypothesis that non-white patients would be significantly less likely than white patients to receive bevacizumab in addition to platinum-based doublet chemotherapy. However, similar to the results from an earlier study[7] of older patients with advanced NSCLC using SEER-Medicare data, blacks were significantly less likely than whites to receive chemotherapy treatment and significantly less likely to receive platinum-based doublet chemotherapy in particular. As a consequence, only a small number of black patients met inclusion criteria for the study, resulting in a lack of sufficient statistical power to identify a significant difference in the use of bevacizumab between blacks and whites. For example, given the sample sizes of whites and blacks and the use of bevacizumab among 6.25% of black patients in the study, more than 11% of white patients needed to have received bevacizumab in order to have a statistically significant difference between blacks and whites with power = 0.8 and alpha = 0.05. On the contrary, only 8.2% of whites received bevacizumab in addition to platinum-based doublet chemotherapy. Therefore, given the limited sample of black patients who received platinum-based doublet chemotherapy, a conclusive evaluation of the use of bevacizumab between blacks and whites could not be made in this study.

To increase sample size and attempt to address the issue of statistical power, blacks could be combined with other non-white patients into one group in order to make a more general comparison of the utilization of bevacizumab between whites and non-whites. However, among patients who

received platinum-based doublet chemotherapy, a greater proportion of non-white patients (9.2%) received bevacizumab than either whites or blacks. As a result, when blacks and other non-whites are combined into one group, the difference in the utilization of bevacizumab between whites and non-whites is smaller than the difference in utilization between whites and blacks. Thus, since the combination of blacks and other non-whites creates a more heterogeneous group of patients than either group alone, comparing the use of bevacizumab between white and non-white patients in this study is not a useful assessment.

Similar to age and race, socioeconomic status variables (i.e., % in census tract aged 25 years and older with less than a high school education and census tract level median household income) were not significantly associated with the use of bevacizumab among patients receiving platinum-based doublet chemotherapy. However, the receipt of any chemotherapy as well as the receipt of platinum-based doublet chemotherapy in particular, differed substantially across quartiles for both education and median household income measures. Patients from census tracts with a lower percentage of individuals with less than a high school education were significantly more likely to receive chemotherapy or platinum-based doublet chemotherapy than patients from census tracts with a higher number of less educated individuals. Likewise, the use of chemotherapy and platinum-based doublet chemotherapy in particular, significantly increased as the census tract level of median household income increased. These differences remained significant even after controlling for important clinical factors such as stage and comorbidity level. Therefore, it appears that treatment differences across socioeconomic status measures exist, but are more likely to involve the decision of whether or not to treat patients with chemotherapy to begin with; once the decision has been made to treat patients with platinum-based doublet chemotherapy, socioeconomic status measures have little influence in the decision of whether or not to add bevacizumab to the first-line chemotherapy regimen.

The most relevant finding from this study was that patients who received 50% or more of their chemotherapy from a provider affiliated with NCI's CCOP were significantly more likely to receive

bevacizumab in addition to platinum-based doublet chemotherapy than patients who received less than half of their chemotherapy from a CCOP-affiliated provider. This result is not all that surprising since the goals of the CCOP include real-world implementation of cancer treatment clinical trials, and the rapid diffusion of novel evidence-based treatments into practice.[43] Considering that bevacizumab received FDA approval for the treatment of advanced NSCLC around the midpoint when patients were diagnosed in this study, it seems reasonable that providers participating in the CCOP, particularly those who accrue and enroll patients in NCI treatment trials, may have earlier and greater exposure to the dissemination of bevacizumab trial results than non-affiliated providers, and therefore would have a greater likelihood of adopting the use of bevacizumab for the treatment of their older patients with advanced non-small cell lung cancer. The finding that receipt of chemotherapy treatment from CCOP-affiliated providers was associated with an increased use of bevacizumab provides empirical evidence to support the CCOP's success in promoting the diffusion of novel, evidence-based treatments into community practice thus providing access to state-of-the-art cancer care among cancer patients in the community setting.

Nevertheless, one cannot delineate from this study whether the greater uptake of bevacizumab among CCOP-affiliated providers is a direct result of the infrastructure provided by the CCOP or the individual characteristics of participating providers. Although the CCOP has established a foundation to enable providers to have quicker and greater access to trial results and novel treatments, providers who participate in the CCOP may be more motivated to seek out current clinical information, engage in innovative practice methods, and/or utilize state-of-the-art therapies than non-participants. Oncologists, irrespective of CCOP affiliation, are likely to gain new clinical knowledge about novel therapies and treatment practices through the provision of clinical guidelines and dissemination of trial results by large professional organizations. For instance, interim results of the ECOG 4599 trial were presented in June 2005 at the ASCO Annual Meeting,[208] following which the National Comprehensive Cancer Network (NCCN) updated its NCCN Clinical Practice Guidelines in Oncology™ for non-small cell lung cancer in October 2005[209] to include the use of bevacizumab plus

chemotherapy as first-line treatment for advanced NSCLC. Thus, knowledge of the effectiveness of bevacizumab was widely disseminated to a broad population of providers well before FDA approval of bevacizumab for NSCLC, suggesting that the early distribution of trial results was not restricted to CCOP-affiliated providers and that the greater use of bevacizumab among patients treated by CCOP-affiliated providers was more likely influenced by the individual characteristics of providers (e.g., greater motivation to engage in innovative treatment practices compared to non-CCOP-affiliated providers) as opposed to the CCOP infrastructure. That is to say, regardless of their participation in the provider-based research network, CCOP-affiliated providers would have been more likely than non-CCOP-affiliated providers to use bevacizumab among their patients.

It is important to point out, however, that the current study did not assess whether receipt of treatment from a CCOP-affiliated provider was associated with greater use of bevacizumab among patients diagnosed before FDA approval, specifically (i.e., patients diagnosed prior to October 2006). The benefit of doing such an analysis would provide some idea about whether the broad dissemination of clinical trial information and practice guidelines influenced the early use of bevacizumab prior to its FDA approval for use in NSCLC. Greater use among patients treated by CCOP-affiliated providers would support the idea that CCOP-affiliated providers are quicker to adapt to changes in clinical guidelines, more willing to adopt novel treatments based solely on early trial results, and are more motivated to engage in state-of-the-art practices (i.e., differences in the early adoption of bevacizumab may be explained by differences in personal characteristics between CCOP-affiliated and non-CCOP-affiliated providers); similar uptake between CCOP-affiliated and non-CCOP-affiliated providers would support the idea that practice guidelines and the dissemination of clinical trial results by professional organizations are as influential in the early adoption of bevacizumab as participation in provider-based research networks. However, restricting the analysis of bevacizumab use to patients diagnosed prior to FDA approval does not provide a complete picture about the association between provider CCOP affiliation and the uptake of bevacizumab. FDA approval of treatments is likely to be an important influence in the utilization of new therapies; less

than 2% of patients diagnosed prior to 2006 received bevacizumab compared to nearly 12% of patients diagnosed in 2006. With the small number of patients receiving bevacizumab prior to FDA approval overall, it is unlikely that utilization differed significantly based on provider affiliation with the CCOP. Conversely, the greater use of bevacizumab observed among patients treated by a CCOP-affiliated provider following FDA approval of bevacizumab for the treatment of advanced NSCLC suggests that even when the dissemination of clinical evidence and practice guidelines is widespread, providers participating in the CCOP are more eager to adopt novel treatments and state-of-the-art practices than non-participating providers.

Apart from year of diagnosis and receipt of chemotherapy treatment from a CCOP-affiliated provider, the utilization of bevacizumab among patients included in this study appeared to be largely influenced by several need or clinical-based characteristics including tumor histology, stage at diagnosis, receipt of radiation treatment, receipt of cancer-directed surgery, the presence of brain metastases, and comorbidity burden. Patients with adenocarcinoma were significantly more likely than patients with tumors of different histology to receive bevacizumab, even after controlling for demographic, clinical, and health care system characteristics in the regression models. A possible explanation for the greater use of bevacizumab among patients with adenocarcinoma histology is that nearly 90% of patients in the ECOG 4599 trial that led to FDA approval of bevacizumab for NSCLC had tumors of adenocarcinoma histology.[188] Thus, oncologists may have felt more comfortable in adding bevacizumab to chemotherapy among older patients with tumor characteristics for which clinical evidence of safety and efficacy had been established.

Standard treatment options for patients with stage IIIB NSCLC include sequential or concurrent chemotherapy and radiation treatment or chemotherapy followed by cancer-directed surgery. Indeed in this study, patients with stage IIIB disease were more likely to receive radiation treatment and more likely to receive cancer-directed surgery than patients with stage IV disease. In addition, stage IIIB patients were significantly less likely to receive bevacizumab in addition to platinum-based doublet chemotherapy as compared to stage IV patients, a finding that may explain (at

least in part) why patients who received radiation treatment and/or cancer-directed surgery were less likely to receive bevacizumab than patients who did not receive either of these therapies. Furthermore, because bevacizumab inhibits angiogenesis, a process involved in wound healing, there is the potential for bevacizumab to contribute to complications in patients undergoing surgery.[210] Given the relatively long half-life of bevacizumab (~20 days), it is commonly recommended that surgery be delayed at least 28 days following the cessation of bevacizumab; similarly, it is not recommended to initiate bevacizumab until at least 28 days following surgery and after complete healing of the surgical wound.[197] Thus, in the current study, bevacizumab may have been avoided in select patients for whom cancer-directed surgery was a potential treatment option because of the necessary delay between the use of bevacizumab and the performance of surgical procedures.

Moreover, the association between bevacizumab and risk of severe hemorrhage as well as the exclusion of patients with brain metastases from the ECOG 4599 trial may explain why patients with brain metastases in the current study were significantly less likely to receive bevacizumab compared to patients without brain metastases. With little or no knowledge about the safety and efficacy of bevacizumab in patients with brain metastases at the time, oncologists may have chosen to be more vigilant in the addition of bevacizumab to platinum-based doublet chemotherapy among these patients until more clinical evidence was available. Similarly, nearly all (~97%) patients with NCI Charlson comorbidity index of 2 had a history of cardiovascular conditions including cerebrovascular disease, congestive heart failure, peripheral vascular disease, and/or myocardial infarction. Further, the ECOG 4599 trial only included patients with a performance status of 0 or 1. Although performance status and the NCI Charlson comorbidity index are not equivalent measures, patients with a comorbidity index of 2 may have been representative of patients with poorer performance status (i.e., > 1). Combined with a concern for severe hemorrhage or other cardiovascular-related complications among a patient population already plagued with cardiovascular conditions, uncertainty regarding the safety and efficacy of bevacizumab among patients with greater comorbidity and/or

poorer performance status may have cautioned oncologists against the use of bevacizumab among these patients.

When all predisposing, enabling, and need characteristics available within the SEER-Medicare database were considered, need characteristics clearly had the largest influence on the utilization of bevacizumab among older patients with advanced NSCLC. In fact, aside from the year of diagnosis and receipt of treatment from a CCOP-affiliated provider, predisposing and enabling characteristics were not associated with the use of bevacizumab. A potential reason for this finding is that patients included in the study were already engaged in a "health service" at the time the decision of whether or not to utilize bevacizumab was made; to be included in the study, patients had to receive platinum-based doublet chemotherapy within four months of diagnosis. Personal determinants of health service use (i.e., predisposing and enabling characteristics such as age, race, and socioeconomic status) may have influenced whether or not patients sought or received chemotherapy to begin with. However, if this is the case, one would expect the subgroup of patients receiving platinum-based doublet chemotherapy to be rather homogenous with regard to predisposing and enabling characteristics compared to the larger overall population with advanced NSCLC. Thus, once engaged in the treatment process, only need/clinical characteristics of the patient (e.g., stage of disease and comorbidity burden) and health care system characteristics (e.g., provider affiliation with the CCOP) are left to differ and potentially influence the use of bevacizumab. Furthermore, given that need characteristics are more likely to influence treatment outcomes than predisposing or enabling characteristics, it is not surprising that these clinical measures had the greatest influence on bevacizumab utilization in this study.

5.2 Effect of Bevacizumab on Survival

The primary objective of this study was to determine whether the utilization of bevacizumab in combination with standard platinum-based doublet chemotherapy as first line treatment of older

adults with advanced NSCLC significantly improved overall survival. In addition, a sub-group analysis was performed to evaluate whether the addition of bevacizumab significantly improved survival among older patients treated first-line with platinum-taxane regimens. Multivariable logistic regression and Cox proportional hazard models were created to assess whether demographic, socioeconomic, or health system characteristics of interest modified any identified effect of bevacizumab on one-year survival or overall survival duration, respectively.

Results from the multivariable models that controlled for observable patient demographic, clinical, and health system characteristics indicated that the addition of bevacizumab to platinum-based doublet chemotherapy did not provide a significant survival advantage over chemotherapy alone. Finding no survival benefit with the use of bevacizumab is consistent with results observed in a subgroup analysis[5] of patients 70 years and older in the ECOG 4599 trial as well as an earlier study[7] of SEER-Medicare data specifically evaluating the effectiveness of adding bevacizumab to carboplatin-paclitaxel. However, differences in overall survival duration between patients in the current study and participants from the subgroup analysis of ECOG 4599 were observed. Median survival duration was shorter among patients in the current study as compared to older clinical participants of the ECOG 4599 trial. In this study, patients receiving bevacizumab in addition to platinum-taxane chemotherapy had a median survival of 10.0 months whereas patients receiving platinum-taxane chemotherapy alone had a median survival of 9.0 months, yielding a survival benefit with bevacizumab of approximately 1 month. In comparison, among older ECOG 4599 trial participants, those receiving bevacizumab in combination with carboplatin-paclitaxel actually had a median survival of 11.3 months vs. 12.1 months for participants receiving carboplatin-paclitaxel alone. Without knowledge from additional analysis, a potential hypothesis for the shorter median survival duration comparing patients in the current study with older participants from the ECOG 4599 trial may be the differences in age distribution across the two studies. Although median age in the current study was 73 years vs. 74 years in the ECOG subgroup analysis, nearly 13% of patients in the current study were 80 years of age or older compared to less than 2% of older participants in ECOG

4599. However, in the current study, the median survival duration of patients aged less than 80 years was no better than the median survival duration of the full cohort. Therefore, distinctions in overall survival duration observed between the current study and the subgroup analysis of elderly participants in ECOG 4599 may be more plausibly explained by differences in comorbidity, performance status, or other influential clinical characteristics not measured or identifiable in SEER-Medicare data.

Subgroup and sensitivity analyses of the effect of bevacizumab on overall survival among patients receiving platinum-based doublet chemotherapy did not lead to results different from those in the original analysis. In the subgroup analysis of patients with stage IV disease, those who received bevacizumab had a more favorable hazard of death compared to patients who received chemotherapy alone, but this finding was not statistically significant. The finding that the hazard ratio estimate in stage IV patients was slightly lower than the hazard ratio observed in the overall cohort is not surprising. Given that patients with stage IV disease were significantly more likely to receive bevacizumab than patients with stage IIIB disease, if patients with stage IIIB have noticeably longer survival duration than stage IV patients, removing stage IIIB patients from the analysis essentially decreases the average overall survival duration among patients receiving platinum-based doublet chemotherapy only while likely having a smaller, if any, effect on the average survival among patients receiving bevacizumab in addition to chemotherapy.

As briefly stated beforehand, age was not significantly associated with survival in the overall cohort. In addition, although older patients (i.e., > 70 years of age) had significantly poorer survival compared to younger patients (i.e., 66-69 years of age) among those receiving platinum-based doublet chemotherapy alone, there was no significant difference in survival across age groups among patients receiving bevacizumab in addition to chemotherapy. An initial assumption for the lack of difference in survival across age groups among patients receiving bevacizumab may be that older patients were similar to younger patients with respect to other measured clinical characteristics that were associated with survival, such as stage at diagnosis and comorbidity level. However, further investigation showed that patients 70 and older receiving bevacizumab were significantly more likely to have an

NCI Charlson comorbidity index greater than 0 and were more likely to have cerebrovascular disease, congestive heart failure, or peripheral vascular disease compared to patients aged 66 to 69 receiving bevacizumab. If greater comorbidity adversely offsets the potential survival benefit of bevacizumab, then a greater difference in survival across age groups among patients receiving bevacizumab would have been expected, with older patients deriving a significantly smaller survival advantage from the use of bevacizumab compared to younger patients. Without knowledge about other clinical factors such as performance status or disease severity, it is difficult to ascertain whether the lack of difference in survival benefit with bevacizumab across age groups is due to unobserved, underlying distinctions between patient groups, differences in secondary treatment, or that the addition of bevacizumab to platinum-based doublet chemotherapy is equally effective (or ineffective) in improving overall survival in older patients with advanced NSCLC, regardless of age.

Race was associated with overall survival in bivariate analyses, but no survival advantage of was observed with the use of bevacizumab among any of the individual categories for race. Still, some survival differences across racial categories were observed within treatment subgroups. For example, whites had significantly poorer survival compared to non-whites among patients treated with chemotherapy alone, although no survival difference was observed between whites and non-whites among patients receiving bevacizumab. It is important to note that because so few blacks and patients of 'other' race groups (i.e. patients not categorized as white or black) met study inclusion criteria and/or received treatment with bevacizumab, this study was not powered to compare the potential survival benefit of bevacizumab between whites and either blacks or other non-white patients.; the distribution of race in this study was similar to that seen in ECOG 4599 where more than 90% of trial participants were categorized as being of white race. Nevertheless, an exploratory analysis comparing the effect of bevacizumab on survival between whites and patients of other non-white race groups, found that patients of other race groups had noticeably longer survival compared to whites. However, there is an absence of clinical information or additional studies in the literature to help explain or support this finding. Given the potential survival advantage with bevacizumab among

patients of other non-white race groups in this study as well as the lack of clinical trial evidence to support or oppose the use of bevacizumab among non-white patients, there is a clear need for future analyses to evaluate the effect of bevacizumab on overall survival in cohorts with relatively larger proportions of minority patient groups.

Similar to race, socioeconomic status variables, including census tract measures of education level and median household income, were significantly associated with overall survival in bivariate analyses, but no survival advantage was observed with the use of bevacizumab among any of the individual quartiles for either education level or median household income. For example, in the bivariate analyses, patients from census tracts categorized in quartiles with the lowest percentage of residents with less than a high school education or the highest median household income had significantly greater survival than patients from census tracts categorized in any other quartile, suggesting that higher education and higher income (i.e. proxies for socioeconomic status) are correlated with improved survival. However, when treatment with bevacizumab was accounted for in the proportional hazards models, neither education level nor median household income remained significantly associated with overall survival. This finding implies that when patients with advanced NSCLC receive similar treatment, survival outcomes are not directly influenced by indicators of patient socioeconomic status.

Whether or not patients received the majority of their chemotherapy treatment from a CCOP-affiliated provider had little relevance on overall survival and did not mediate any association between bevacizumab and survival either. For example, among patients who received treatment from a CCOP-affiliated provider, there was no significant difference in overall survival when comparing patients who received bevacizumab with patient who received platinum-based doublet chemotherapy alone. In addition, among patients who received bevacizumab, those patients who were treated by a CCOP-affiliated provider did not fare any better with respect to overall survival than patients who were not treated by a CCOP-affiliated provider. Thus, although patients treated by CCOP-affiliated

providers were more likely to receive bevacizumab in addition to platinum-based doublet chemotherapy, they did not appear to derive any significant survival advantage because of it.

A notable finding in this study was that overall survival significantly differed between men and women, regardless of treatment received. For instance, among patients receiving platinum-based doublet chemotherapy alone, women had significantly longer survival than men. Similarly, women also had considerably longer survival than men among patients receiving bevacizumab in addition to platinum-based doublet chemotherapy. However, when the effect of bevacizumab on survival was assessed within each sex, neither women nor men exhibited a significant difference. A likely explanation for the overall difference in survival between sexes is that men were significantly more likely to have greater comorbidity than women; approximately 42% of men had an NCI Charlson comorbidity index > 0 compared to about 36% of women with more than 6% of men having an index of 2 vs. less than 4% of women.

In addition to tumor stage, several other clinical characteristics including tumor histology, receipt of radiation treatment, receipt of cancer-directed surgery, the presence of brain metastases, and comorbidity burden were significantly associated with overall survival in bivariate analyses, though they did not influence the effect of bevacizumab on survival. For instance, patients with adenocarcinoma generally had longer overall survival than patients with tumors of different histology. However, among patients receiving bevacizumab, overall survival duration did not differ significantly across tumor histology categories, even when histology was categorized dichotomously as adenocarcinoma and non-adenocarcinoma. Similarly, among patients with adenocarcinoma tumors, receipt of bevacizumab was not significantly associated with improved survival. This latter finding is in contrast to a subgroup analysis of ECOG 4599 that evaluated the effect of bevacizumab by tumor histology.[188] Among trial participants with adenocarcinoma in the subgroup analysis, the combination of bevacizumab with carboplatin-paclitaxel chemotherapy was associated with a significant increase in overall survival compared to carboplatin-paclitaxel alone. Interestingly, among patients with adenocarcinoma in the current study, those who received bevacizumab were significantly more likely

to have an NCI Charlson index of zero compared to patients receiving chemotherapy alone, yet no survival advantage with bevacizumab was observed.

5.3 Effect of Bevacizumab on Hospitalization for Severe Adverse Events

The primary objective of this study was to determine whether the utilization of bevacizumab in combination with standard platinum-based doublet chemotherapy as first line treatment of older adults with advanced NSCLC was associated with a significant increase in hospitalizations for severe treatment-related adverse events including, arterial thromboembolic events, gastrointestinal perforation, neutropenia, and severe hemorrhage. In addition, sub-group analyses were performed to evaluate whether the addition of bevacizumab to platinum-based doublet chemotherapy significantly increased the risk of hospitalization for severe adverse events among patients stratified by NCI Charlson comorbidity index or among patients specifically treated first-line with carboplatin-paclitaxel chemotherapy. Multivariable logistic regression models were created to assess whether demographic, socioeconomic, or health system characteristics of interest modified any identified effect of bevacizumab on the odds of hospitalization for severe adverse events during the first 180 days of treatment. Likewise, multivariable Cox proportional hazard models were performed to evaluate whether the same characteristics influenced any identified association between bevacizumab and the hazard of hospitalization within the identified first-line treatment window.

Over the first 180 days of treatment, patients receiving bevacizumab in combination with platinum-based doublet chemotherapy had significantly greater cumulative incidence of hospitalization for gastrointestinal perforation and hospitalization for any severe adverse event compared to patients receiving platinum-based doublet chemotherapy alone. By comparison, when evaluation of hospitalization for severe adverse events was restricted to the duration of the first-line treatment window, only the cumulative incidence of hospitalization for any severe adverse events was significantly higher among patients receiving bevacizumab compared to patients receiving

chemotherapy alone. Lastly, the overall cumulative incidence of hospitalization for severe adverse events with the use of bevacizumab did not vary significantly across key independent variables of interest including age, race, and the census tract level measures of education and median household income.

In general, although direct comparisons cannot be made because of differences in the way adverse events were measured and identified between studies, the incidence rates of hospitalization for severe adverse events in this study were not unlike the rates of adverse events reported in clinical trials and other observational studies. For example, in both the current study and the subgroup analysis of older participants in ECOG 4599,[5] irrespective of treatment, 3% to 4% of patients experienced significant hemorrhage. Similarly, though gastrointestinal perforation has not been evaluated in clinical trials for bevacizumab in NSCLC, the cumulative incidence of 1% to 2% among patients in the current study is consistent with findings from clinical[211,212] and observational[213,214] studies of gastrointestinal perforation with the use of bevacizumab in metastatic colorectal cancer. However, the cumulative incidence rates of arterial thromboembolic events and neutropenia identified in this study were lower than the rates reported in the subgroup analysis of ECOG 4599. Given that these incidence rates were lower among both treatment groups (i.e., patients receiving or not receiving bevacizumab), it seems plausible that the distinctions between studies are due to differences in the way these adverse events were identified and measured.

Overall, results from multivariable logistic regression models evaluating the effect of bevacizumab on the odds of hospitalization for severe adverse events during the first 180 days of chemotherapy treatment were similar to unadjusted results. Among patients receiving any platinum-based doublet chemotherapy, those patients who also received bevacizumab were at significantly increased risk for hospitalization for gastrointestinal perforation after controlling for additional characteristics (peripheral vascular disease and brain metastases). However, the increased risk of hospitalization for gastrointestinal perforation with the use of bevacizumab was not statistically significant among patients receiving platinum-taxane chemotherapy in particular. Among patients

receiving platinum-taxane chemotherapy, only the risk of hospitalization for any severe adverse event was significantly increased with the use of bevacizumab. Still, it is important to note that some of the hospitalizations detected during the first 180 days of treatment occurred well after the cessation of first-line treatment. In addition, there is the possibility that some of the hospitalizations identified were not related to chemotherapy or bevacizumab treatment. Thus, it is not possible to establish causality between treatment and hospitalization in this analysis and therefore the findings of increased odds of hospitalization for gastrointestinal perforation or any severe adverse event with the use of bevacizumab should be interpreted cautiously.

Restricting the evaluation of hospitalization for severe adverse events to the duration of first-line treatment may provide a better picture of the potential relationship between bevacizumab and the risk of the specified adverse events than observation over the first 6 months of treatment. Although results between the analyses were generally similar, in multivariable Cox proportional hazard models evaluating the effect of bevacizumab on the hazard of hospitalization for severe adverse events during the first-line treatment window, utilization of bevacizumab was not significantly associated with hospitalization for any of the severe adverse events. However, the hazard ratio estimates in the multivariable-adjusted models did suggest that the hazard of hospitalization for each of the adverse events is elevated with the use of bevacizumab in comparison to chemotherapy alone. Again, this is consistent with results from the ECOG 4599 trial[56] which found a significant increase in the incidence of neutropenia and bleeding events among trial participants receiving bevacizumab-carboplatin-paclitaxel; severe bleeding, but not neutropenia, was significantly elevated among participants receiving bevacizumab-carboplatin-paclitaxel in the subgroup analysis of older patients in ECOG 4599.[5]

5.4 Implications of Study

Results from the current study have potentially important implications with respect to the treatment of older patients with advanced non-small cell lung cancer. In general, the utilization of bevacizumab in addition to standard platinum-based doublet chemotherapy was relatively low. The low use of bevacizumab can be explained in part due to the time at which many patients in the cohort were diagnosed and treated relative to the time when bevacizumab was approved by the FDA for use in combination with chemotherapy in the treatment of advanced NSCLC. Utilization of bevacizumab increased following the dissemination of initial clinical trial results and revision of NCCN guidelines to recommend bevacizumab plus chemotherapy as first-line treatment of advanced NSCLC in mid-to-late 2005 followed by FDA approval of bevacizumab in October 2006. Still, less than 25% of patients receiving platinum-based doublet chemotherapy in the calendar year following the FDA's approval also received bevacizumab at the start of treatment. This suggests that many oncologists are prudent in their use of newer anti-cancer therapies, particularly treatments without published evidence of their efficacy in specific populations such as older adults.

In relation to the uptake of bevacizumab, a key finding in this study was the greater utilization of bevacizumab among patients who received a majority of their chemotherapy from a provider affiliated with the National Cancer Institute's Community Clinical Oncology Program. The CCOP provides a research network among community oncologists where newly developed cancer interventions can be evaluated through clinical trials populated by patients recruited through participating physicians. In addition, CCOP allows for rapid dissemination of new findings and quick diffusion of new evidence-based therapies throughout the research network. Ideally, community oncologists engaged in CCOP stay well-informed about and have convenient access to evidence-based information on novel cancer interventions. In turn, CCOP-affiliated oncologists, through clinical trial recruitment and implementation of these novel interventions, provide rapid adoption of innovative changes to cancer prevention and treatment in the community setting. Considering the

wide dissemination of clinical trial results purporting the effectiveness of bevacizumab by both ASCO and the NCCN and the initiation of treatment in nearly half of the patients included in this study prior to FDA approval for advanced NSCLC, current study results provide clear evidence of a more rapid adoption of bevacizumab among CCOP-affiliated providers and successful promotion of access to state-of-the-art cancer care in the community setting among Medicare patients with advanced NSCLC.

Future studies should delineate the specific determinants of the greater uptake of bevacizumab by CCOP-affiliated providers to determine whether the adoption of this novel treatment by CCOP participants was influenced by the individual characteristics of providers, the underlying infrastructure of the CCOP, or a combination of the two. This knowledge will inform policymakers about how to further improve the diffusion and uptake of innovative treatments in the community setting by establishing whether provider characteristics (e.g., the motivation to engage in innovative treatment practices) and or organizational/practice-site characteristics (e.g., system-level access to new clinical information and/or novel therapies) differ between CCOP and non-CCOP participants. In turn, this will allow policymakers to determine whether efforts to improve the dissemination of information and adoption of novel treatments should be focused on promoting greater community provider participation in the CCOP, establishing additional opportunities for community providers to stay informed and gain access to new therapies (particularly for those unable to participate in the CCOP), and/or encouraging community providers who may otherwise be less motivated to seek out current clinical trial results, engage in novel practice methods, or adopt state-of-the-art treatments.

In addition to the greater use of bevacizumab among patients treated by CCOP-affiliated providers, another important finding in this study was the lack of age, race, and socioeconomic disparities in the use of bevacizumab among patients receiving platinum-based doublet chemotherapy. An earlier evaluation[15] of patients with advanced NSCLC in the SEER-Medicare database found significantly decreased use of any chemotherapy among older patients, patients of black race (as compared to whites), and patients of lower socioeconomic status (as measured by

census tract level of median household income). Older patients and black patients were also significantly less likely to receive platinum-based doublet regimens as compared to younger patients and white patients, respectively. The current study found similar differences as older patients, patients of black race, and patients of lower socioeconomic status were significantly less likely to receive any chemotherapy and black patients and patients of lower socioeconomic status were less likely to receive platinum-based doublet regimens. Thus, important disparities continue to exist in regards to the decision to initiate chemotherapy. However, the results of the current study suggest that once oncologists and their patients have committed to pursuing chemotherapeutic treatment with platinum-based doublet chemotherapy, the decision to add bevacizumab to the treatment regimen is not influenced by patient age, race, or proxy measures of socioeconomic status.

Despite positive findings with regards to its utilization, the absence of a clear survival advantage with bevacizumab when added to standard platinum-based doublet chemotherapy among this cohort of Medicare beneficiaries raises concern about its future utility in the treatment of older patients with advanced NSCLC. Previous subgroup analysis of older participants in ECOG 4599 and an earlier observational cohort study of SEER-Medicare both reported no significant improvement in overall survival with the addition of bevacizumab to carboplatin-paclitaxel chemotherapy. The results of the current study further extrapolate this finding among a cohort of Medicare beneficiaries treated first-line with a broader range of platinum-based doublet chemotherapy regimens. Furthermore, when the cost of adding bevacizumab to standard platinum-based doublet chemotherapy is considered, the relative absence of a survival advantage among older patients with advanced NSCLC brings additional doubt as to the cost-effectiveness of this novel therapy.[215]

Still, as some patients receiving bevacizumab in the current study survived 2 or more years beyond the start of treatment, it is possible that there are older adults who have derived significant benefit from the receipt of bevacizumab. However, determining whether specific individuals survived longer specifically because of the receipt of bevacizumab during first-line treatment is not possible without additional information. This unknown gap in information can create a conundrum for

companies or agencies that administer health insurance plans such as the Centers for Medicare and Medicaid Services (CMS) as they make policy decisions with respect to the coverage of novel treatments. In the case of bevacizumab, use of this new agent adds significant cost to treatment which the health plan assists in paying for, and there is a lack of evidence to support its effectiveness in improving survival among a population sample of older adults with advanced NSCLC. However, as just mentioned, it is possible that some individuals benefit significantly from the use of bevacizumab. Thus, in the absence of additional information, health plans may be forced to decide whether to continue coverage at the risk of incurring significant additional treatment costs with the possibility that patients do not actually derive any benefit, or to discontinue coverage in part or in whole at the risk of denying some patients access to a treatment that they would otherwise benefit from. Interestingly, this is a dilemma that the CMS faced recently with regards to bevacizumab; despite a decision in 2011 by the FDA to revoke the breast cancer indication of bevacizumab because of safety and effectiveness concerns, the CMS chose to maintain coverage of bevacizumab in the treatment of patients with metastatic breast cancer. Therefore, given that bevacizumab has maintained its indication for the first-line treatment of advanced non-squamous non-small cell lung cancer with platinum-based chemotherapy, evidence from clinical trials showing that bevacizumab improves overall survival, progression-free survival, and treatment response rates in the larger population of patients with advanced NSCLC, and the precedent set forth by CMS in its coverage of bevacizumab in the treatment of metastatic breast cancer, health insurance plans should retain coverage of bevacizumab in the treatment of advanced NSCLC regardless of patient age. In addition, to discourage overutilization of bevacizumab and unnecessary increases in overall treatment costs, health plans should consider implementing additional policies that restrict coverage of bevacizumab to patients who demonstrate a potential to derive benefit from its use (e.g., patients receiving platinum-based doublet chemotherapy, patients with low comorbidity burden, etc.).

Policymakers responsible for developing treatment guidelines and practicing oncologists also face similar dilemmas regarding the utility of bevacizumab. Policymakers must utilize available

evidence from clinical trials and observational studies that assess the availability, efficacy/effectiveness, and safety of treatment alternatives when making therapeutic recommendations for populations of affected patients. Oncologists face the challenge of making individual treatment decisions (such as whether or not to add bevacizumab to first-line chemotherapy) based on whether or not they think their patient will benefit at the point of care. Overall results of clinical trials clearly show improvements in survival and treatment response with the addition of bevacizumab to platinum-based chemotherapy in the treatment of advanced NSCLC. However, results from the current study as well as those from the previous literature including subgroup analyses of older clinical trial participants consistently indicate that bevacizumab does not provide a survival benefit to older patients. Without additional knowledge beyond what has been described in this study and the previous literature, differentiating subpopulations of patients or individuals who are most likely to benefit from the receipt of bevacizumab may be extremely challenging. However, the recent development of a prognostic model[216] based on information from ECOG 4599 may prove useful to oncologists as a clinical decision tool and to researchers as an instrument to further evaluate and understand the effectiveness of bevacizumab in advanced NSCLC. Still, until there is additional empirical evidence to support the use of bevacizumab among patients based on specific clinical characteristics, guidelines should restrict the recommendation of bevacizumab as a first-line treatment option to those patients with characteristics representative of those observed in clinical trials, e.g., patients who are younger, have a good performance status (0 or 1), adenocarcinoma histology, and are treated with platinum-based doublet chemotherapy. Similarly, the use of bevacizumab should not be recommended by guidelines as a standard component of care in the treatment of older adults with advanced NSCLC based on evidence indicating older patients derive no survival benefit from its use. Nevertheless, individual oncologists should not restrict the use of bevacizumab based on patient age alone; although the broad use of bevacizumab among older adults is not recommended, oncologists should use bevacizumab sensibly based on clinical characteristics and preferences of the individual patient and knowledge of outcomes observed among similar patients.

Finally, although estimates were not statistically significant, the hazard of hospitalization for severe treatment-related adverse events including arterial thromboembolic events, gastrointestinal perforation, neutropenia, and severe hemorrhage appears to be elevated with the use of bevacizumab. Furthermore, the hazards of hospitalization for neutropenia and any severe adverse event were significantly increased with the use of bevacizumab among patients with greater comorbidity; additional caution is warranted when making treatment decisions regarding the use of bevacizumab in patients who may be at greater risk of complications at baseline. Combined with added cost of treatment and uncertainty about its effectiveness in improving survival beyond that of standard platinum-based doublet chemotherapy, the potential of increased risk for severe treatment-related adverse events necessitates prudent use of bevacizumab among older patients with advanced NSCLC.

5.5 Limitations and Ideas for Further Study

Results of this study must be interpreted with several limitations in mind that are characteristic of observational studies, particularly those that utilize data collected from administrative health care claims. First, inclusion and exclusion criteria restricted the study cohort to Medicare fee-for-service beneficiaries with a primary cancer diagnosis of advanced NSCLC on or after the age of 66 who were living in a SEER region at the time of diagnosis. Therefore, the cohort derived for this study may not be representative of all older patients with advanced NSCLC in the United States,[196] although the study cohort is probably more representative than the sample of older participants from ECOG 4599. Nevertheless, results from the study may not be generalizable to Medicare patients enrolled in an HMO, diagnosed with another form of cancer previous or simultaneous to their diagnosis of NSCLC, diagnosed before the age of 66, or living outside of a SEER region at the time of diagnosis. Careful consideration of these limitations to the generalizability of the study findings is necessary before attempting to extrapolate the results to a broader population of patients with advanced NSCLC. Future research should consider evaluating the utilization and

effectiveness of bevacizumab among Medicare beneficiaries enrolled in an HMO as well as those diagnosed outside of the SEER regions to gain a fuller understanding of its use and utility in a broader population of older adults with advanced NSCLC.

A second limitation of this study involves the absence of clinical details and patient behaviors within the SEER-Medicare database, such as performance status, genetic and molecular markers, disease severity, baseline lung function, treatment dose, tumor response, patient smoking status, and patient preferences for treatment. These variables may be highly associated with the selection of treatment, overall survival, the incidence of severe treatment-related adverse events, or a combination thereof. Inability to identify and account for these potential associations may lead to residual bias in the effect estimates for bevacizumab. However, it is probable that patients in worse overall health (i.e., poor performance status and/or poor baseline lung function) would have been selected for treatment without bevacizumab and therefore, under the assumption these patients have shorter survival duration, we would expect the difference in survival to be larger (perhaps significantly) between those patients receiving bevacizumab and those not. Similarly, if patients in poorer overall health are more susceptible to severe treatment-related adverse events and are selected into treatment without bevacizumab, we would expect the difference in hospitalization for adverse events between those receiving bevacizumab and those not to be relatively smaller. The fact that large differences in survival or hospitalization for specific treatment-related adverse events were not observed provides confidence that the effect estimates for bevacizumab in the current study were not overly biased from the lack of information on important clinical characteristics. In addition, results from propensity score-adjusted models and sensitivity analyses confirmed the robustness of the study findings. Nonetheless, the potential for selection bias due to unmeasured confounders should not be discounted when interpreting the results of the current study.

A possible solution to account for residual bias in observational studies is instrumental variable analysis, a methodology widely used in econometrics that can account for both observed and unobserved measures. The key to instrumental variable analysis is the identification of at least one

variable that is associated with treatment selection but is exogenous to the measured outcome other than through its association with the treatment. Essentially, the goal of instrumental variable analysis is to mimic the randomization process used in clinical trials; patients receive different treatments in accordance with varying values of the instrument, but treatment groups are similar across other observed and unobserved characteristics of patients. This study attempted instrumental variable analysis using two potential instruments including receipt of treatment from a CCOP-affiliated provider and a lagged measure of Health Service Area[217] use of bevacizumab. However, neither variable successfully met the criteria for a good instrument. For example, despite having a significant association with bevacizumab and no direct link to overall survival, receipt of treatment from a CCOP-affiliated provider was significantly related to other observed patient characteristics, including those associated with treatment outcomes; thus, it is plausible that unobserved characteristics would not have been well balanced across treatment groups using receipt of treatment from a CCOP-affiliated provider as an instrument. Furthermore, although measurement of Health Service Area (HSA) utilization of bevacizumab among patients diagnosed in 2004-2006 was an independent predictor of bevacizumab use among patients diagnosed in 2007 (i.e., higher HSA utilization of bevacizumab in 2004-2006 was significantly associated with greater use of bevacizumab among patients diagnosed in 2007), it was also predictive of patient mortality (i.e., low HSA utilization of bevacizumab in 2004-2006 was significantly associated with poorer survival among patients diagnosed in 2007). Given the potential for residual bias from unobserved characteristics that could not be accounted for in the current study, future research should identify and validate the prognostic value of additional clinical and patient behavior measures with respect to the utilization, safety, and effectiveness of bevacizumab. In addition, given the similar survival times between patients receiving and patients not receiving bevacizumab, additional outcome measures such as the quality of life over the survival period may be valuable in further evaluating the effectiveness of bevacizumab and identifying its utility in the treatment of older adults with advanced NSCLC.

A third limitation to consider is the possibility of measurement error with the operationalization of several variables including census tract measures of education attainment and median household income, race, and comorbidity status. The absence of patient level socioeconomic data in SEER necessitated the application of aggregate, census tract level information for each individual although it is possible that such information is not representative of an individual's true education level or household income. Likewise, comorbidity was measured using a validated algorithm and health care claims data. Although this method has been used extensively in the literature, there are limitations in using administrative claims data to assess comorbidity including the lack of capture of diagnoses and services outside of the health plan. However, it is unlikely that any potential measurement errors were unevenly distributed across treatment groups. Moving forward, future research may consider alternative data sources with richer and more valid information on patient level socioeconomic measures, race and ethnicity, and specific comorbid diseases along with the levels of disease severity.

The fourth limitation of this study that warrants discussion is the restriction of cases to patients diagnosed through 2007. As has been previously mentioned, bevacizumab did not receive FDA approval for the treatment of advanced NSCLC until late 2006. Therefore, without a significant uptake of bevacizumab in the treatment of Medicare fee-for-service beneficiaries diagnosed within SEER regions, the cohort of patients receiving bevacizumab in this study was destined to be relatively small. It is possible that studies with more recently diagnosed patients and/or larger samples of older adults may come up with results different from the current analysis. Future evaluation of bevacizumab within a larger cohort of patients, particularly one that includes a larger sample of non-white patients as well as more recently diagnosed cases, would be informative in developing a greater understanding of the safety and effectiveness of bevacizumab in older adults with advanced NSCLC.

Finally, a fifth limitation to consider when interpreting the results of this study is that subsequent treatment may have influenced survival. For example, some patients not receiving bevacizumab first-line may have received it during subsequent treatment and this may have prolonged

their survival beyond that of patients never receiving bevacizumab at all. Patients who received bevacizumab subsequent to first-line therapy were categorized in the platinum-based chemotherapy only group and therefore, if they derived longer survival from the use of secondary treatment with bevacizumab, this may narrow the measured effect of bevacizumab on survival between patients receiving and not receiving bevacizumab during initial treatment, particularly if all other patients in the analysis derived no additional benefit from other secondary treatments. A potential solution to this situation is to control for the subsequent use of bevacizumab or exclude patients receiving subsequent bevacizumab treatment from the analysis. However, this would take away from the intent-to-treat approach of the current analysis and further limit the generalizability of the results. In addition, such an analysis may not be practical to oncologists as it is unlikely they would attempt to predict which patients are candidates for secondary treatment with bevacizumab (or any other agent) at the time initial treatment decisions are being made. However, future studies may want to evaluate the effects of subsequent treatment on survival outcomes following initial treatment with bevacizumab, when and where subsequent treatment can be clearly delineated and measured.

5.6 Conclusions

The objectives of this study were to determine the utilization, effectiveness, and safety of adding bevacizumab to standard platinum-based doublet chemotherapy in the treatment of Medicare fee-for-service beneficiaries with advanced NSCLC. This study showed that the utilization of bevacizumab among older patients was largely driven by clinical characteristics including stage, histology, and comorbidity level. In addition, greater utilization of bevacizumab among older patients receiving chemotherapy treatment through CCOP-affiliated physicians provides evidence of the rapid diffusion and uptake of novel therapies by oncologists engaged in community-based clinical research networks. However, this study also confirmed previous findings that the addition of bevacizumab to standard platinum-based doublet chemotherapy does not provide a discernible survival advantage

over chemotherapy alone in the treatment of advanced NSCLC in Medicare beneficiaries. With no clear survival benefit detected among older adults in clinical trials or observational study analyses, and the potential for increased harm with the use of bevacizumab supports the argument that bevacizumab is not suitable as a standard therapy in the first-line treatment of older patients with advanced NSCLC. Without additional evidence to support its safety and effectiveness in the Medicare population, oncologists should reserve the use of bevacizumab to patients in whom they believe there will be clear benefit.

APPENDIX A

ADMINISTRATIVE DIAGNOSTIC AND PROCEURAL CODES FOR ADVERSE EVENTS

Table A-1. Administrative diagnostic and procedural codes used to identify hospitalization for specific adverse events of interest

Adverse event	Definition	Specific administrative codes for relevant conditions
ATE	Presence of an ***inpatient*** administrative claim with at least one ICD-9-CM diagnosis code suggesting the presence of a severe arterial thromboembolic event requiring hospitalization	**ICD-9-CM Diagnosis:** 410.xx 413.xx 415.1 415.11 430 431 432 432.0 432.1 432.9 433.01 433.11 433.21 433.31 433.81 433.91 434 434.0 434.01 434.1 434.11 434.9 434.91 435 435.8 435.9 V12.54
GI perforation	Presence of an ***inpatient*** administrative claim with at least one ICD-9-CM diagnosis code OR one ICD-9-CM operative procedure code OR one CPT code indicating a diagnosis or surgical procedure suggesting the presence of gastrointestinal perforation	**ICD-9-CM Diagnosis:** 531.1 531.10 531.11 531.2 531.20 531.21 532.1 532.2 533.1 533.2 534.1 534.2 569.83 863.1 863.3 863.5 863.9 **ICD-9-CM Diagnostic Procedure:** 88.01 88.02 **ICD-9-CM Operative Procedure**: 17.31 45.61 45.62 45.71 45.72 45.74 45.9 46.1 46.10 46.11 46.13 46.2 46.7 46.79 47.0 47.01 47.09 **CPT:** 43361 44120 44121 44125 44126 44127 44128 44130 44140 44144 44145 44202 44203 44204 44205 44227 44602 44603 44604 44605 44620 44625 44626 74150 74160 74170 74176 74177 74178
Neutropenia	Presence of an ***inpatient*** administrative claim with at least one ICD-9-CM diagnosis code suggesting the presence of severe neutropenia requiring hospitalization	**ICD-9-CM Diagnosis:** 288.xx (includes any code beginning with 288)
Severe hemorrhage	Presence of an ***inpatient*** administrative claim with at least one ICD-9-CM diagnosis code suggesting the presence of a severe bleeding event requiring hospitalization	**ICD-9-CM Diagnosis:** 430 431 432 432.0 432.1 432.9 459.0 530.82 531.0 531.2 531.4 531.6 532.0 532.2 532.4 532.6 533.0 533.2 533.4 533.6 534.0 534.2 534.4 534.6 535.01 535.11 535.21 535.41 535.51 535.61 535.71 537.83 562.02 562.03 562.12 562.13 569.3 569.85 578 578.0 578.9 623.8 626.8 784.7 784.8 786.3 786.30 786.39

Abbreviations: ICD-9-CM = International Classification of Diseases, 9th revision, Clinical Modification; CPT = Common Procedural Terminology; ATE = Arterial thromboembolic events; GI = Gastrointestinal.

APPENDIX B

HIERARCHICAL ANALYSIS OF THE USE OF BEVACIZUMAB

Table B-1. Multivariate associations of predisposing characteristics on the odds of bevacizumab use among patients receiving platinum-based doublet chemotherapy

Characteristic	Adjusted OR	95% CI	p-value
Predisposing			
Age			0.411
66 to 69	ref		
70 to 79	0.88	(0.70, 1.11)	
80 and older	0.80	(0.56, 1.15)	
Sex			0.466
Female	ref		
Male	0.92	(0.74, 1.14)	
Marital status			0.140
Not married	ref		
Married	1.19	(0.94, 1.49)	
Race			0.518
White	ref		
Black	0.78	(0.47, 1.29)	
Other	1.13	(0.72, 1.78)	
% 25 years and older in census tract w/ < HS education			0.568
Lowest quartile	ref		
Second	0.85	(0.63, 1.10)	
Third	0.83	(0.66, 1.15)	
Highest	0.87	(0.63, 1.16)	

Abbreviations: OR = Odds ratio; CI = Confidence interval; HS = High school.

Table B-2. Multivariate associations of predisposing and enabling characteristics on the odds of bevacizumab use among patients receiving platinum-based doublet chemotherapy

Characteristic	Adjusted OR	95% CI	p-value
Predisposing			
Age			0.244
66 to 69	ref		
70 to 79	0.86	(0.67, 1.10)	
80 and older	0.73	(0.50, 1.08)	
Sex			0.283
Female	ref		
Male	0.88	(0.70, 1.11)	
Marital status			0.115
Not married	ref		
Married	1.22	(0.95, 1.56)	
Race			0.381
White	ref		
Black	0.71	(0.42, 1.21)	
Other	1.13	(0.67, 1.91)	
% 25 years and older in census tract w/ < HS education			0.655
Lowest quartile	ref		
Second	0.89	(0.64, 1.22)	
Third	0.82	(0.56, 1.19)	
Highest	0.75	(0.47, 1.20)	
Enabling			
Median household income (census tract level)			0.655
Lowest quartile	ref		
Second	0.83	(0.57, 1.20)	
Third	0.77	(0.49, 1.22)	
Highest	0.85	(0.52, 1.40)	
Population density			0.290
Urban/Rural	ref		
Metro	1.21	(0.85, 1.74)	
State buy-in Medicare coverage during year preceding diagnosis			0.837
No	ref		
Yes	0.96	(0.62, 1.48)	
≥ 50% of chemotherapy claims from CCOP provider			<0.001
No	ref		
Yes	1.62	(1.25, 2.10)	

Table B-2 (Continued)

Year of diagnosis			<0.001
2004-2005	ref		
2006	7.77	(5.43, 11.12)	
2007	12.55	(8.83, 17.83)	
SEER region			0.209
East	ref		
Midwest	1.62	(0.78, 1.69)	
South	1.40	(1.01, 1.93)	
West	1.25	(0.87, 1.81)	

Abbreviations: OR = Odds ratio; CI = Confidence interval; HS = High school; CCOP = Clinical Community Oncology Program.

Table B-3. Multivariate associations of predisposing characteristics on the odds of bevacizumab use among patients receiving platinum-taxane doublet chemotherapy

Characteristic	Adjusted OR	95% CI	p-value
Predisposing			
Age			0.310
66 to 69	ref		
70 to 79	0.92	(0.71, 1.19)	
80 and older	1.05	(0.49, 1.09)	
Sex			0.736
Female	ref		
Male	1.25	(0.76, 1.21)	
Marital status			0.221
Not married	ref		
Married	1.51	(0.91, 1.50)	
Race			0.305
White	ref		
Black	1.27	(0.58, 1.63)	
Other	1.80	(0.90, 2.34)	
% 25 years and older in census tract w/ < HS education			0.131
Lowest quartile	ref		
Second	1.34	(0.55, 1.01)	
Third	1.20	(0.55, 1.01)	
Highest	1.20	(0.53, 1.04)	

Abbreviations: OR = Odds ratio; CI = Confidence interval; HS = High school.

Table B-4. Multivariate associations of predisposing and enabling characteristics on the odds of bevacizumab use among patients receiving platinum-taxane doublet chemotherapy

Characteristic	OR	95% CI	p-value
Predisposing			
Age			0.304
66 to 69	ref		
70 to 79	0.89	(0.68, 1.18)	
80 and older	0.72	(0.47, 1.10)	
Sex			0.487
Female	ref		
Male	0.92	(0.71, 1.18)	
Marital status			0.189
Not married	ref		
Married	1.20	(0.92, 1.57)	
Race			0.312
White	ref		
Black	0.92	(0.53, 1.60)	
Other	1.53	(0.87, 2.69)	
% 25 years and older in census tract w/ < HS education			0.483
Lowest quartile	ref		
Second	0.81	(0.57, 1.15)	
Third	0.74	(0.49, 1.12)	
Highest	0.71	(0.42, 1.19)	
Enabling			
Median household income (census tract level)			0.773
Lowest quartile	ref		
Second	0.96	(0.63, 1.47)	
Third	0.87	(0.53, 1.43)	
Highest	1.04	(0.60, 1.81)	
Population density			0.337
Urban/Rural	ref		
Metro	1.21	(0.82, 1.80)	
State buy-in Medicare coverage during year preceding diagnosis			0.750
No	ref		
Yes	0.92	(0.57, 1.51)	
≥ 50% of chemotherapy claims from CCOP provider			0.002
No	ref		
Yes	1.57	(1.19, 2.08)	

Table B-4 (continued)

Year of diagnosis			<0.001
2004-2005	ref		
2006	8.34	(5.65, 12.31)	
2007	13.16	(8.96, 19.32)	
SEER region			0.147
East	ref		
Midwest	1.29	(0.84, 1.98)	
South	1.52	(1.06, 2.16)	
West	1.34	(0.89, 2.01)	

Abbreviations: OR = Odds ratio; CI = Confidence interval; HS = High school; CCOP = Clinical Community Oncology Program.

APPENDIX C

BIVARIATE ASSOCIATIONS WITH OVERALL SURVIVAL AMONG PATIENTS RECEIVING PLATINUM-TAXANE CHEMOTHERAPY

Table C-1. Bivariate associations between overall survival and predisposing, enabling, and need characteristics among patients receiving platinum-taxane doublet chemotherapy

Characteristic	No. of patients	Median survival time Months (95% CI)	*P*	HR (95% CI)
Predisposing				
Age at diagnosis			0.083	
66 to 69	886	9.7 (8.87, 10.37)		ref
70 to 79	2069	8.9 (8.33, 9.50)		1.07 (0.99, 1.16)
80 and older	446	8.8 (7.73, 9.80)		1.14 (1.01, 1.28)
Sex			< 0.001	
Female	1599	10.3 (9.77, 10.90)		ref
Male	1802	8.1 (7.60, 8.67)		1.29 (1.20, 1.38)
Marital Status			0.284	
Not married	1296	8.7 (8.03, 9.37)		ref
Married	2105	9.4 (8.77, 9.87)		0.96 (0.89, 1.03)
Race/Ethnicity			0.002	
White	3040	8.9 (8.50, 9.37)		ref
Black	202	9.6 (8.07, 11.00)		0.96 (0.83, 1.12)
Other	159	14.4 (10.47, 16.37)		0.74 (0.62, 0.87)
% 25 years and older in census tract w/ < HS education			0.092	
Lowest quartile	915	9.5 (8.53, 10.23)		ref
Second	891	8.9 (8.33, 9.70)		1.04 (0.95, 1.15)
Third	886	9.4 (8.37, 10.20)		1.04 (0.95, 1.15)
Highest	703	8.7 (7.70, 9.43)		1.14 (1.03, 1.26)
Enabling				
Median household income (census tract level)			0.080	
Lowest quartile	737	9.4 (8.57, 10.07)		ref
Second	849	8.6 (7.70, 9.33)		1.04 (0.94, 1.16)
Third	883	8.8 (8.00, 9.73)		1.01 (0.91, 1.12)
Highest	930	9.8 (8.73, 10.53)		0.92 (0.83, 1.02)

Table C-1 (Continued)

Population density			0.571	
Urban/rural	528	9.2 (8.37, 10.07)		ref
Metro	2873	9.1 (8.60, 9.53)		0.97 (0.88, 1.07)
State buy-in Medicare coverage during year preceding diagnosis			0.637	
No	3121	9.1 (8.70, 9.57)		ref
Yes	280	8.7 (7.47, 10.73)		0.97 (0.85, 1.10)
≥ 50% of chemotherapy claims from CCOP-affiliated provider			0.455	
No	2493	8.9 (8.43, 9.43)		ref
Yes	782	9.5 (8.67, 10.07)		0.97 (0.89, 1.05)
Received treatment from provider affiliated with a cooperative research group			0.002	
No	1411	8.3 (7.70, 8.77)		ref
Yes	1742	9.7 (9.10, 10.07)		0.89 (0.83, 0.96)
Year of diagnosis			0.413	
2004-2005	1693	8.7 (8.20, 9.33)		ref
2006	914	9.5 (8.50, 10.33)		0.95 (0.87, 1.03)
2007	794	9.5 (8.73, 10.47)		0.97 (0.89, 1.06)
SEER region			0.286	
East	823	9.5 (8.57, 10.27)		ref
Midwest	623	8.4 (7.40, 9.43)		1.09 (0.98, 1.22)
South	1322	8.9 (8.37, 9.67)		1.02 (0.94, 1.12)
West	633	9.5 (8.53, 10.33)		0.98 (0.88, 1.09)
Need				
Tumor stage			< 0.001	
IIIB	1020	12.8 (11.87, 14.03)		ref
IV	2381	7.8 (7.40, 8.30)		1.50 (1.39, 1.62)
Summary stage			< 0.001	
Regional	318	16.0 (14.23, 19.00)		ref
Distant	3083	8.7 (8.23, 9.10)		1.65 (1.46, 1.86)
Grade			< 0.001	
Well/Moderately differentiated	406	12.1 (10.57, 14.10)		ref
Poor/Undifferentiated	985	8.3 (7.60, 9.00)		1.44 (1.28, 1.63)
Unknown	2010	8.9 (8.43, 9.50)		1.40 (1.25, 1.56)
Tumor histology			0.003	
Adenocarcinoma	1930	9.7 (9.13, 10.17)		ref
Large cell	180	8.5 (6.97, 10.67)		1.12 (0.97, 1.31)
Other and NOS	1291	8.3 (7.73, 8.87)		1.14 (1.06, 1.22)

Table C-1 (Continued)

NCI Charlson Comorbidity Index			< 0.001	
0	2029	9.4 (8.77, 9.90)		ref
1	1117	9.1 (8.47, 9.77)		1.10 (1.03, 1.19)
2	173	6.8 (5.03, 8.57)		1.46 (1.26, 1.69)
Hemoptysis			0.980	
No	3255	9.1 (8.67, 9.57)		ref
Yes	146	9.1 (7.63, 10.07)		0.99 (0.84, 1.17)
Brain metastases			< 0.001	
No	2580	9.1 (8.60, 9.67)		ref
Yes	821	9.1 (8.13, 9.77)		1.14 (1.06, 1.23)
Radiation therapy received			0.019	
No	1603	9.9 (9.37, 10.57)		ref
Yes	1747	8.5 (7.93, 8.93)		1.08 (1.01, 1.15)
Cancer-directed surgery			< 0.001	
No	3157	8.7 (8.27, 9.10)		ref
Yes	225	19.2 (14.50, 23.57)		0.46 (0.39, 0.54)

Abbreviations: CI = Confidence interval; HR = Hazard ratio; CCOP = Clinical Community Oncology Program; SEER = Surveillance, Epidemiology, and End Results; NOS = Not otherwise specified; NCI = National Cancer Institute.

APPENDIX D

MULTIVARIABLE-ADJUSTED ASSOCIATIONS WITH OVERALL SURVIVAL

Table D-1. Multivariable-adjusted model evaluating the effects of the use of bevacizumab and all predisposing, enabling, and need characteristics on overall survival among patients receiving platinum-based doublet chemotherapy.

	Any platinum-based doublet (n = 4746)	**Platinum-taxane doublet (n = 3401)**
Characteristic	HR (95% CI)	HR (95% CI)
Bevacizumab		
No	Ref	ref
Yes	1.00 (0.88, 1.13)	0.99 (0.86, 1.13)
Predisposing		
Age at diagnosis		
66 to 69	ref	ref
70 to 79	1.07 (0.99, 1.14)	1.07 (0.99, 1.16)
80 and older	1.13 (1.03, 1.24)	1.15 (1.03, 1.28)
Sex		
Female	ref	ref
Male	1.31 (1.24, 1.38)	1.30 (1.22, 1.38)
Marital Status		
Not married	ref	ref
Married	0.90 (0.83, 0.97)	0.89 (0.81, 0.98)
Race		
White	ref	ref
Black	0.92 (0.78, 1.06)	0.91 (0.75, 1.08)
Other	0.76 (0.60, 0.92)	0.72 (0.52, 0.91)
% 25 years and older in census tract w/ < HS education		
Lowest quartile	ref	ref
Second	1.06 (0.97, 1.15)	1.02 (0.90, 1.13)
Third	1.10 (0.99, 1.21)	0.99 (0.86, 1.12)
Highest	1.16 (1.03, 1.30)	1.08 (0.92, 1.24)
Enabling		
Median household income (census tract level)		
Lowest quartile	ref	ref
Second	1.08 (0.98, 1.19)	1.08 (0.95, 1.21)
Third	1.06 (0.94, 1.18)	1.05 (0.90, 1.20)
Highest	1.04 (0.90, 1.18)	1.00 (0.83, 1.17)

Table D-1 (Continued)

Population density		
Urban/rural	ref	ref
Metro	1.01 (0.91, 1.11)	1.03 (0.91, 1.15)
State buy-in Medicare coverage during year preceding diagnosis		
No	ref	ref
Yes	0.92 (0.80, 1.05)	0.93 (0.78, 1.08)
≥ 50% of chemotherapy claims from CCOP provider		
No	ref	ref
Yes	0.97 (0.89, 1.05)	0.99 (0.90, 1.09)
Received treatment from provider affiliated with a cooperative group affiliation		
No	ref	ref
Yes	0.91 (0.84, 0.98)	0.89 (0.81, 0.97)
Year of diagnosis		
2004-2005	ref	ref
2006	0.92 (0.84, 1.00)	0.93 (0.84, 1.02)
2007	0.94 (0.86, 1.03)	0.94 (0.83, 1.04)
SEER region		
East	ref	ref
Midwest	1.05 (0.95, 1.15)	1.04 (0.92, 1.17)
South	1.10 (0.99, 1.20)	1.08 (0.95, 1.20)
West	1.04 (0.95, 1.13)	1.04 (0.94, 1.15)
Need		
Tumor stage		
IIIB	ref	ref
IV	1.49 (1.42, 1.56)	1.52 (1.43, 1.60)
Grade		
Well/Moderately differentiated	ref	ref
Poor/Undifferentiated	1.32 (1.21, 1.44)	1.28 (1.14, 1.42)
Unknown	1.16 (1.05, 1.27)	1.17 (1.04, 1.30)
Tumor histology		
Adenocarcinoma	ref	ref
Large cell	1.02 (0.87, 1.16)	1.02 (0.85, 1.19)
Other and NOS	0.99 (0.92, 1.06)	1.02 (0.94, 1.10)

Table D-1 (Continued)

NCI Charlson Comorbidity Index		
0	ref	ref
1	1.04 (0.98, 1.11)	0.99 (0.91, 1.08)
2	1.37 (1.22, 1.51)	1.43 (1.26, 1.60)
Hemoptysis		
No	ref	ref
Yes	1.05 (0.89, 1.21)	1.10 (0.92, 1.28)
Brain metastases		
No	ref	ref
Yes	1.09 (1.01, 1.17)	1.08 (0.99, 1.17)
Radiation therapy received		
No	ref	ref
Yes	1.06 (0.99, 1.13)	1.06 (0.99, 1.14)
Cancer-directed surgery		
No	ref	ref
Yes	0.49 (0.32, 0.65)	0.48 (0.28, 0.68)

Abbreviations: CI = Confidence interval; HR = Hazard ratio; CCOP = Clinical Community Oncology Program; SEER = Surveillance, Epidemiology, and End Results; NOS = Not otherwise specified; NCI = National Cancer Institute.

APPENDIX E

CHARCTERISTICS OF PATIENTS MATCHED ON ESTIMATED PROPENSITY SCORES FOR RECEIPT OF BEVACIZUMAB (FOR OVERALL SURVIVAL ANALYSIS)

Table E-1. Baseline characteristics among patients matched on estimated propensity score for receipt of bevacizumab, n (%)

	Platinum-based doublet chemotherapy			Platinum-taxane doublet chemotherapy		
	Bevacizumab			Bevacizumab		
Characteristic	Yes (n = 346)	No (n = 346)	*P*	Yes (n = 300)	No (n = 300)	*P*
Predisposing						
Age at diagnosis			0.030			0.425
66 to 69	98 (28.3)	76 (22.0)		80 (26.7)	88 (29.3)	
70 to 79	211 (61.0)	213 (61.6)		189 (63.0)	174 (58.0)	
80 and older	37 (10.7)	57 (16.5)		31 (10.3)	38 (12.7)	
Sex			0.704			0.935
Female	168 (48.6)	163 (47.1)		157 (52.3)	158 (52.7)	
Male	178 (51.4)	183 (52.9)		143 (47.7)	142 (47.3)	
Marital Status			0.020			0.238
Not married	121 (35.0)	151 (43.6)		105 (35.0)	119 (39.7)	
Married	225 (65.0)	195 (56.4)		195 (65.0)	181 (60.3)	
Race			0.456			0.806
White	308 (89.0)	314 (90.8)		263 (87.7)	268 (89.3)	
Black	18 (5.2)	19 (5.5)		18 (6.0)	15 (5.0)	
Other	20 (5.8)	13 (3.8)		19 (6.3)	17 (5.7)	

Table E-1 (Continued)

% 25 years and older in census tract w/ < HS education			0.239			0.298
Lowest quartile	114 (32.9)	132 (38.2)		103 (34.3)	83 (27.7)	
Second	87 (25.1)	91 (26.3)		74 (24.7)	80 (26.7)	
Third	82 (23.7)	62 (17.9)		69 (23.0)	83 (27.7)	
Highest	63 (18.2)	61 (17.6)		54 (18.0)	53 (17.7)	
Enabling						
Median household income (census tract level)			0.216			0.882
Lowest quartile	71 (20.5)	56 (16.2)		59 (19.7)	62 (20.7)	
Second	82 (23.7)	84 (24.3)		71 (23.7)	63 (21.0)	
Third	84 (24.3)	89 (25.7)		73 (24.3)	77 (25.7)	
Highest	109 (31.5)	117 (33.8)		97 (32.3)	98 (32.7)	
Population density			0.654			0.198
Urban/rural	44 (12.7)	48 (13.9)		37 (12.3)	48 (16.0)	
Metro	302 (87.3)	298 (86.1)		263 (87.7)	252 (84.0)	
State buy-in Medicare coverage during year preceding diagnosis			0.309			0.322
No	317 (91.6)	324 (93.6)		276 (92.0)	269 (89.7)	
Yes	29 (8.4)	22 (6.4)		24 (8.0)	31 (10.3)	
≥ 50% of chemotherapy claims from CCOP-affiliated provider			0.174			0.057
No	242 (69.9)	258 (74.6)		205 (68.3)	226 (75.3)	
Yes	104 (30.1)	88 (25.4)		95 (31.7)	74 (24.7)	

Table E-1 (Continued)

Received treatment from provider affiliated with a:						
Cooperative research group			0.316			0.805
No	151 (43.6)	138 (39.9)		133 (44.3)	130 (43.3)	
Yes	195 (56.4)	208 (60.1)		167 (55.7)	170 (56.7)	
Teaching hospital			0.885			0.679
No	155 (44.8)	154 (44.5)		139 (46.3)	145 (48.3)	
Yes	189 (54.6)	192 (55.5)		159 (53.0)	155 (51.7)	
Year of diagnosis			<0.001			<0.001
2004-2005	37 (10.7)	195 (56.4)		31 (10.3)	158 (52.7)	
2006	135 (39.0)	197 (56.9)		121 (40.3)	75 (25.0)	
2007	174 (50.3)	54 (15.6)		148 (49.3)	67 (22.3)	
SEER region			0.952			0.280
East	62 (17.9)	64 (18.5)		54 (18.0)	71 (23.7)	
Midwest	72 (20.8)	73 (21.1)		62 (20.7)	50 (16.7)	
South	69 (19.9)	63 (18.2)		59 (19.7)	61 (20.3)	
West	143 (41.3)	146 (42.2)		125 (41.7)	118 (39.3)	
Need						
Tumor stage			0.099			0.914
IIIB	64 (18.5)	48 (13.9)		53 (17.7)	52 (17.3)	
IV	282 (81.5)	298 (86.1)		237 (79.0)	248 (82.7)	
Summary stage			0.506			0.505
Regional	12 (3.5)	9 (2.6)		9 (3.0)	12 (4.0)	
Distant	334 (96.5)	337 (97.4)		291 (97.0)	288 (96.0)	
Grade			0.267			0.833
Well/Moderately differentiated	44 (12.7)	31 (9.0)		36 (12.0)	33 (11.0)	
Poor/Undifferentiated	90 (26.0)	90 (26.0)		76 (25.3)	72 (24.0)	
Unknown	212 (61.3)	225 (65.0)		188 (62.7)	195 (65.0)	

Table E-1 (Continued)

Tumor histology			0.270			0.971
Adenocarcinoma	231 (66.8)	212 (61.3)		198 (66.0)	198 (66.0)	
Large cell	11 (3.2)	10 (2.9)		9 (3.0)	10 (3.3)	
Other and NOS	104 (30.1)	124 (35.8)		93 (31.0)	92 (30.7)	
NCI Charlson Comorbidity Index			0.919			0.863
0	231 (66.8)	226 (65.3)		205 (68.3)	211 (70.3)	
1	106 (30.6)	111 (32.1)		89 (29.7)	83 (27.7)	
2	9 (2.6)	9 (2.6)		6 (2.0)	6 (2.0)	
Hemoptysis			0.009			0.794
No	338 (97.7)	324 (93.6)		292 (97.3)	293 (97.7)	
Yes	8 (2.3)	22 (6.4)		8 (2.7)	7 (2.3)	
Brain metastases			0.916			0.824
No	293 (84.7)	292 (84.4)		251 (83.7)	253 (84.3)	
Yes	53 (15.3)	54 (15.6)		49 (16.3)	47 (15.7)	
Radiation therapy received			0.803			0.659
No	244 (70.5)	241 (69.7)		209 (69.7)	204 (68.0)	
Yes	102 (29.5)	105 (30.3)		91 (30.3)	96 (32.0)	
Cancer-directed surgery			0.994			0.190
No	333 (96.2)	332 (96.0)		291 (97.0)	284 (94.7)	
Yes	12 (3.5)	12 (3.5)		8 (2.7)	14 (4.7)	

Abbreviations: CCOP = Clinical Community Oncology Program; SEER = Surveillance, Epidemiology, and End Results; NOS = Not otherwise specified; NCI = National Cancer Institute.

APPENDIX F

ADDITIONAL ANALYSES OF THE ASSOCIATION BETWEEN BEVACIZUMAB AND HOSPITALIZATION FOR SEVERE TREATMENT-RELATED ADVERSE EVENTS

Table F-1.Multivariable-adjusted models evaluating the effect of bevacizumab on the odds of hospitalization for severe adverse events within 180 days of treatment start while controlling for predisposing, enabling, and need characteristics

Adverse event	Any platinum doublet OR (95% CI)	Platinum-taxane doublet OR (95% CI)
Arterial thromboembolic events		
Multivariable adjusted models		
Predisposing	0.65 (0.30, 1.40)	0.69 (0.30, 1.61)
Enabling	0.61 (0.28, 1.34)	0.65 (0.27, 1.53)
Need	0.74 (0.34, 1.62)	0.81 (0.35, 1.91)
Predisposing, enabling, and need	0.73 (0.33, 1.64)	0.82 (0.34, 2.01)
Gastrointestinal perforation		
Multivariable adjusted models		
Predisposing	2.24 (1.09, 4.62)	2.19 (1.00, 4.80)
Enabling	2.71 (1.18, 6.19)	2.71 (1.08, 6.76)
Need	2.29 (1.09, 4.81)	2.13 (0.95, 4.76)
Predisposing, enabling, and need	2.83 (1.20, 6.71)	2.64 (1.01, 6.85)
Neutropenia		
Multivariable adjusted models		
Predisposing	1.20 (0.85, 1.70)	1.25 (0.59, 1.81)
Enabling	1.12 (0.77, 1.64)	1.22 (0.82, 1.83)
Need	1.20 (0.83, 1.74)	1.19 (0.79, 1.77)
Predisposing, enabling, and need	1.13 (0.76, 1.69)	1.17 (0.76, 1.81)
Severe hemorrhage		
Multivariable adjusted models		
Predisposing	1.00 (0.60, 1.67)	1.04 (0.59, 1.84)
Enabling	0.95 (0.55, 1.64)	1.16 (0.64, 2.11)
Need	1.01 (0.59, 1.72)	1.07 (0.59, 1.95)
Predisposing, enabling, and need	1.00 (0.56, 1.78)	1.24 (0.65, 2.36)
Any severe adverse event		
Multivariable adjusted models		
Predisposing	1.30 (0.99, 1.72)	1.40 (1.03, 1.89)
Enabling	1.22 (0.91, 1.65)	1.36 (0.98, 1.87)
Need	1.32 (0.99, 1.78)	1.38 (1.01, 1.90)
Predisposing, enabling, and need	1.27 (0.93, 1.75)	1.38 (0.98, 1.96)

Abbreviations: HR = Hazard ratio; CI = Confidence interval.

Table F-2. Multivariable-adjusted models evaluating the effect of bevacizumab on the hazard of hospitalization for severe adverse events during the first-line treatment window while controlling for predisposing, enabling, and need characteristics

Adverse event	Any platinum doublet HR (95% CI)	Platinum-taxane doublet HR (95% CI)
Arterial thromboembolic events		
Multivariable adjusted models		
Predisposing	1.24 (0.51, 2.61)	1.58 (0.58, 3.68)
Enabling	1.12 (0.42, 2.65)	1.87 (0.58, 5.61)
Need	1.08 (0.44, 2.29)	1.36 (0.50, 3.16)
Predisposing, enabling, and need	0.96 (0.33, 2.45)	2.71 (0.72, 9.95)
Gastrointestinal perforation		
Multivariable adjusted models		
Predisposing	2.76 (1.04, 6.41)	2.13 (0.71, 5.55)
Enabling	2.36 (0.78, 6.50)	1.61 (0.46, 5.02)
Need	2.14 (0.84, 4.85)	1.86 (0.65, 4.65)
Predisposing, enabling, and need	4.57 (1.18, 17.05)	0.64 (0.05, 5.37)
Neutropenia		
Multivariable adjusted models		
Predisposing	1.35 (0.91, 1.95)	1.48 (0.96, 2.18)
Enabling	1.26 (0.81, 1.89)	1.32 (0.83, 2.04)
Need	1.10 (0.71, 1.64)	1.11 (0.70, 1.68)
Predisposing, enabling, and need	1.12 (0.68, 1.75)	1.12 (0.66, 1.81)
Severe hemorrhage		
Multivariable adjusted models		
Predisposing	1.48 (0.83, 2.45)	1.77 (0.95, 3.05)
Enabling	1.18 (0.63, 2.05)	1.64 (0.84, 3.03)
Need	1.44 (0.79, 2.45)	1.63 (0.85, 2.89)
Predisposing, enabling, and need	1.13 (0.58, 2.08)	1.85 (0.88, 3.73)
Any severe adverse event		
Multivariable adjusted models		
Predisposing	1.56 (1.16, 2.05)	1.71 (1.25, 2.29)
Enabling	1.35 (0.97, 1.83)	1.51 (1.07, 2.10)
Need	1.39 (1.01, 1.86)	1.39 (1.00, 1.90)
Predisposing, enabling, and need	1.26 (0.89, 1.76)	1.37 (0.93, 1.96)

Abbreviations: HR = Hazard ratio; CI = Confidence interval

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10-29. doi: 10.3322/caac.20138; 10.3322/caac.20138.

2. Altekruse S, Kosary C, Krapcho M, et al. SEER cancer statistics review, 1975-2007. http://seer.cancer.gov/csr/1975_2007/. Published 2010. Updated 2010. Accessed March, 5, 2011.

3. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: The TAX 326 study group. *J Clin Oncol*. 2003;21(16):3016-3024. doi: 10.1200/JCO.2003.12.046.

4. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008;26(21):3543-3551. doi: 10.1200/JCO.2007.15.0375.

5. Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: Analysis of Eastern Cooperative Oncology Group trial 4599. *J Clin Oncol*. 2008;26(1):60-65. doi: 10.1200/JCO.2007.13.1144.

6. Leighl NB, Zatloukal P, Mezger J, et al. Efficacy and safety of bevacizumab-based therapy in elderly patients with advanced or recurrent nonsquamous non-small cell lung cancer in the phase III BO17704 study (AVAiL). *J Thorac Oncol*. 2010;5(12):1970-1976. doi: 10.1097/JTO.0b013e3181f49c22.

7. Zhu J, Sharma DB, Gray SW, Chen AB, Weeks JC, Schrag D. Carboplatin and paclitaxel with vs without bevacizumab in older patients with advanced non-small cell lung cancer. *JAMA*. 2012;307(15):1593-1601. doi: 10.1001/jama.2012.454.

8. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst*. 2011;103(2):117-128. doi: 10.1093/jnci/djq495.

9. Bradley CJ, Yabroff KR, Dahman B, Feuer EJ, Mariotto A, Brown ML. Productivity costs of cancer mortality in the United States: 2000-2020. *J Natl Cancer Inst*. 2008;100(24):1763-1770. doi: 10.1093/jnci/djn384.

10. Surveillance Research Program, National Cancer Institute. Fast stats: An interactive tool for access to SEER cancer statistics. http://seer.cancer.gov/faststats. Accessed July 15, 2011.

11. Hutchins LF, Unger JM, Crowley JJ, Coltman CA,Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med*. 1999;341(27):2061-2067. doi: 10.1056/NEJM199912303412706.

12. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: Race-, sex-, and age-based disparities. *JAMA*. 2004;291(22):2720-2726. doi: 10.1001/jama.291.22.2720.

13. Ford JG, Howerton MW, Lai GY, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: A systematic review. *Cancer*. 2008;112(2):228-242. doi: 10.1002/cncr.23157.

14. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol*. 2003;21(7):1383-1389.

15. Davidoff AJ, Tang M, Seal B, Edelman MJ. Chemotherapy and survival benefit in elderly patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2010;28(13):2191-2197. doi: 10.1200/JCO.2009.25.4052.

16. Hardy D, Xia R, Liu CC, Cormier JN, Nurgalieva Z, Du XL. Racial disparities and survival for nonsmall-cell lung cancer in a large cohort of black and white elderly patients. *Cancer*. 2009;115(20):4807-4818. doi: 10.1002/cncr.24521.

17. Wisnivesky JP, McGinn T, Henschke C, Hebert P, Iannuzzi MC, Halm EA. Ethnic disparities in the treatment of stage I non-small cell lung cancer. *Am J Respir Crit Care Med*. 2005;171(10):1158-1163. doi: 10.1164/rccm.200411-1475OC.

18. Hardy D, Liu CC, Xia R, et al. Racial disparities and treatment trends in a large cohort of elderly black and white patients with nonsmall cell lung cancer. *Cancer*. 2009;115(10):2199-2211. doi: 10.1002/cncr.24248.

19. Smith CB, Bonomi M, Packer S, Wisnivesky JP. Disparities in lung cancer stage, treatment and survival among American Indians and Alaskan Natives. *Lung Cancer*. 2011;72(2):160-164. doi: 10.1016/j.lungcan.2010.08.015.

20. Shugarman LR, Mack K, Sorbero ME, et al. Race and sex differences in the receipt of timely and appropriate lung cancer treatment. *Med Care*. 2009;47(7):774-781. doi: 10.1097/MLR.0b013e3181a393fe.

21. Flenaugh EL, Henriques-Forsythe MN. Lung cancer disparities in African Americans: Health versus health care. *Clin Chest Med*. 2006;27(3):431-9, vi. doi: 10.1016/j.ccm.2006.04.006.

22. Fesinmeyer MD, Goulart B, Blough DK, Buchwald D, Ramsey SD. Lung cancer histology, stage, treatment, and survival in American Indians and Alaska Natives and whites. *Cancer*. 2010;116(20):4810-4816. doi: 10.1002/cncr.25410.

23. Farjah F, Wood DE, Yanez ND,3rd, et al. Racial disparities among patients with lung cancer who were recommended operative therapy. *Arch Surg*. 2009;144(1):14-18. doi: 10.1001/archsurg.2008.519.

24. Bryant AS, Cerfolio RJ. Impact of race on outcomes of patients with non-small cell lung cancer. *J Thorac Oncol*. 2008;3(7):711-715. doi: 10.1097/JTO.0b013e31817c60c7.

25. Bach PB, Cramer LD, Warren JL, Begg CB. Racial differences in the treatment of early-stage lung cancer. *N Engl J Med*. 1999;341(16):1198-1205. doi: 10.1056/NEJM199910143411606.

26. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin*. 2011;61(4):212-236. doi: 10.3322/caac.20121.

27. Cykert S, Dilworth-Anderson P, Monroe MH, et al. Factors associated with decisions to undergo surgery among patients with newly diagnosed early-stage lung cancer. *JAMA*. 2010;303(23):2368-2376. doi: 10.1001/jama.2010.793.

28. Garrett BE, Dube SR, Trosclair A, Caraballo RS, Pechacek TF, Centers for Disease Control and Prevention (CDC). Cigarette smoking - United States, 1965-2008. *MMWR Surveill Summ*. 2011;60 Suppl:109-113.

29. Blackstock AW, Herndon JE,2nd, Paskett ED, et al. Similar outcomes between African American and non-African American patients with extensive-stage small-cell lung carcinoma: Report from the Cancer and Leukemia Group B. *J Clin Oncol*. 2006;24(3):407-412. doi: 10.1200/JCO.2005.02.1436.

30. Schwartz KL, Crossley-May H, Vigneau FD, Brown K, Banerjee M. Race, socioeconomic status and stage at diagnosis for five common malignancies. *Cancer Causes Control*. 2003;14(8):761-766.

31. Earle CC, Neumann PJ, Gelber RD, Weinstein MC, Weeks JC. Impact of referral patterns on the use of chemotherapy for lung cancer. *J Clin Oncol*. 2002;20(7):1786-1792.

32. Margolis ML, Christie JD, Silvestri GA, Kaiser L, Santiago S, Hansen-Flaschen J. Racial differences pertaining to a belief about lung cancer surgery: Results of a multicenter survey. *Ann Intern Med*. 2003;139(7):558-563.

33. McCann J, Artinian V, Duhaime L, Lewis JW,Jr, Kvale PA, DiGiovine B. Evaluation of the causes for racial disparity in surgical treatment of early stage lung cancer. *Chest*. 2005;128(5):3440-3446. doi: 10.1378/chest.128.5.3440.

34. Clegg LX, Reichman ME, Miller BA, et al. Impact of socioeconomic status on cancer incidence and stage at diagnosis: Selected findings from the Surveillance, Epidemiology, and End Results: National longitudinal mortality study. *Cancer Causes Control*. 2009;20(4):417-435. doi: 10.1007/s10552-008-9256-0.

35. Yorio JT, Yan J, Xie Y, Gerber DE. Socioeconomic disparities in lung cancer treatment and outcomes persist within a single academic medical center. *Clin Lung Cancer*. 2012;13(6):448-457. doi: 10.1016/j.cllc.2012.03.002; 10.1016/j.cllc.2012.03.002.

36. Halasz LM, Weeks JC, Neville BA, Taback N, Punglia RS. Use of stereotactic radiosurgery for brain metastases from non-small cell lung cancer in the United States. *Int J Radiat Oncol Biol Phys*. 2012. doi: 10.1016/j.ijrobp.2012.08.007; 10.1016/j.ijrobp.2012.08.007.

37. Erhunmwunsee L, Joshi MB, Conlon DH, Harpole DH,Jr. Neighborhood-level socioeconomic determinants impact outcomes in nonsmall cell lung cancer patients in the Southeastern United States. *Cancer*. 2012;118(20):5117-5123. doi: 10.1002/cncr.26185; 10.1002/cncr.26185.

38. Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P. In lung cancer patients, age, race-ethnicity, gender and smoking predict adverse comorbidity, which in turn predicts treatment and survival. *J Clin Epidemiol*. 2004;57(6):597-609. doi: 10.1016/j.jclinepi.2003.11.002.

39. Bouchardy C, Fioretta G, De Perrot M, Obradovic M, Spiliopoulos A. Determinants of long term survival after surgery for cancer of the lung: A population-based study. *Cancer*. 1999;86(11):2229-2237.

40. Stavraky KM, Skillings JR, Stitt LW, Gwadry-Sridhar F. The effect of socioeconomic status on the long-term outcome of cancer. *J Clin Epidemiol*. 1996;49(10):1155-1160.

41. Earle CC, Venditti LN, Neumann PJ, et al. Who gets chemotherapy for metastatic lung cancer? *Chest*. 2000;117(5):1239-1246.

42. National Cancer Institute. About the community clinical oncology program. http://dcp.cancer.gov.libproxy.lib.unc.edu/programs-resources/programs/ccop/about/history. Accessed November 18, 2012.

43. Minasian LM, Carpenter WR, Weiner BJ, et al. Translating research into evidence-based practice: The National Cancer Institute Community Clinical Oncology Program. *Cancer*. 2010;116(19):4440-4449. doi: 10.1002/cncr.25248.

44. McAlearney AS, Song PH, Reiter KL. Why providers participate in clinical trials: Considering the National Cancer Institute's Community Clinical Oncology Program. *Contemp Clin Trials*. 2012;33(6):1143-1149. doi: 10.1016/j.cct.2012.08.008; 10.1016/j.cct.2012.08.008.

45. Witt RL, Frelick RW. Head and neck cancer care at a community-based teaching hospital. *Head Neck*. 2005;27(7):613-615. doi: 10.1002/hed.20194.

46. Carpenter WR, Meyer AM, Wu Y, et al. Translating research into practice: The role of provider-based research networks in the diffusion of an evidence-based colon cancer treatment innovation. *Med Care*. 2012;50(8):737-748. doi: 10.1097/MLR.0b013e31824ebe13.

47. Carpenter WR, Reeder-Hayes K, Bainbridge J, et al. The role of organizational affiliations and research networks in the diffusion of breast cancer treatment innovation. *Med Care*. 2011;49(2):172-179. doi: 10.1097/MLR.0b013e3182028ff2.

48. Laliberte L, Fennell ML, Papandonatos G. The relationship of membership in research networks to compliance with treatment guidelines for early-stage breast cancer. *Med Care*. 2005;43(5):471-479.

49. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: Analysis of the Surveillance, Epidemiologic, and End Results database. *J Clin Oncol*. 2006;24(28):4539-4544. doi: 10.1200/JCO.2005.04.4859.

50. Jackman DM, Johnson BE. Small-cell lung cancer. *Lancet*. 2005;366(9494):1385-1396. doi: 10.1016/S0140-6736(05)67569-1.

51. Yang P, Allen MS, Aubry MC, et al. Clinical features of 5,628 primary lung cancer patients: Experience at Mayo Clinic from 1997 to 2003. *Chest*. 2005;128(1):452-462. doi: 10.1378/chest.128.1.452.

52. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655.

53. Finkelstein DM, Ettinger DS, Ruckdeschel JC. Long-term survivors in metastatic non-small-cell lung cancer: An Eastern Cooperative Oncology Group study. *J Clin Oncol*. 1986;4(5):702-709.

54. Slebos RJ, Kibbelaar RE, Dalesio O, et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. *N Engl J Med*. 1990;323(9):561-565. doi: 10.1056/NEJM199008303230902.

55. Azzoli CG, Baker S,Jr, Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol*. 2009;27(36):6251-6266. doi: 10.1200/JCO.2009.23.5622.

56. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355(24):2542-2550. doi: 10.1056/NEJMoa061884.

57. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2004;22(11):2184-2191. doi: 10.1200/JCO.2004.11.022.

58. Hardy D, Xia R, Liu CC, Cormier JN, Nurgalieva Z, Du XL. Racial disparities and survival for nonsmall-cell lung cancer in a large cohort of black and white elderly patients. *Cancer*. 2009;115(20):4807-4818. doi: 10.1002/cncr.24521.

59. Obasaju CK, Ansari RH, Socinski MA, et al. A comparison of white and African American outcomes from a three-arm, randomized, phase III multicenter trial of advanced or metastatic non-small cell lung cancer. *J Thorac Oncol*. 2010;5(7):993-1000.

60. Graham MV, Geitz LM, Byhardt R, et al. Comparison of prognostic factors and survival among black patients and white patients treated with irradiation for non-small-cell lung cancer. *J Natl Cancer Inst*. 1992;84(22):1731-1735.

61. Greenwald HP, Polissar NL, Borgatta EF, McCorkle R, Goodman G. Social factors, treatment, and survival in early-stage non-small cell lung cancer. *Am J Public Health*. 1998;88(11):1681-1684.

62. Yang R, Cheung MC, Byrne MM, et al. Do racial or socioeconomic disparities exist in lung cancer treatment? *Cancer*. 2010;116(10):2437-2447. doi: 10.1002/cncr.24986.

63. Blackstock AW, Herndon JE,2nd, Paskett ED, et al. Outcomes among African-American/non-African-American patients with advanced non-small-cell lung carcinoma: Report from the Cancer and Leukemia Group B. *J Natl Cancer Inst*. 2002;94(4):284-290.

64. Albain KS, Unger JM, Crowley JJ, Coltman CA,Jr, Hershman DL. Racial disparities in cancer survival among randomized clinical trials patients of the Southwest Oncology group. *J Natl Cancer Inst*. 2009;101(14):984-992. doi: 10.1093/jnci/djp175.

65. Herbst RS, Lynch TJ, Sandler AB. Beyond doublet chemotherapy for advanced non-small-cell lung cancer: Combination of targeted agents with first-line chemotherapy. *Clin Lung Cancer*. 2009;10(1):20-27. doi: 10.3816/CLC.2009.n.003.

66. Carbone D. Smoking and cancer. *Am J Med*. 1992;93(1A):13S-17S.

67. Alberg AJ, Samet JM. Epidemiology of lung cancer. *Chest*. 2003;123(1 Suppl):21S-49S.

68. Doll R, Peto R, Boreham J, Sutherland I. Mortality from cancer in relation to smoking: 50 years observations on British doctors. *Br J Cancer*. 2005;92(3):426-429. doi: 10.1038/sj.bjc.6602359.

69. Cataldo JK, Dubey S, Prochaska JJ. Smoking cessation: An integral part of lung cancer treatment. *Oncology*. 2010;78(5-6):289-301. doi: 10.1159/000319937.

70. Rice D, Kim HW, Sabichi A, et al. The risk of second primary tumors after resection of stage I nonsmall cell lung cancer. *Ann Thorac Surg*. 2003;76(4):1001-7; discussion 1007-8.

71. Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: Systematic review of observational studies with meta-analysis. *BMJ*. 2010;340:b5569. doi: 10.1136/bmj.b5569.

72. Zhang J, Kamdar O, Le W, Rosen GD, Upadhyay D. Nicotine induces resistance to chemotherapy by modulating mitochondrial signaling in lung cancer. *Am J Respir Cell Mol Biol*. 2009;40(2):135-146. doi: 10.1165/rcmb.2007-0277OC.

73. Xu J, Huang H, Pan C, Zhang B, Liu X, Zhang L. Nicotine inhibits apoptosis induced by cisplatin in human oral cancer cells. *Int J Oral Maxillofac Surg*. 2007;36(8):739-744. doi: 10.1016/j.ijom.2007.05.016.

74. Stewart A, King A, Killen J, Ritter P. Does smoking cessation improve health-related quality of life? *Ann Behav Med*. 1995;17(4):331-338.

75. Garces YI, Yang P, Parkinson J, et al. The relationship between cigarette smoking and quality of life after lung cancer diagnosis. *Chest*. 2004;126(6):1733-1741. doi: 10.1378/chest.126.6.1733.

76. Baser S, Shannon VR, Eapen GA, et al. Smoking cessation after diagnosis of lung cancer is associated with a beneficial effect on performance status. *Chest*. 2006;130(6):1784-1790. doi: 10.1378/chest.130.6.1784.

77. Fox JL, Rosenzweig KE, Ostroff JS. The effect of smoking status on survival following radiation therapy for non-small cell lung cancer. *Lung Cancer*. 2004;44(3):287-293. doi: 10.1016/j.lungcan.2003.11.012.

78. Subramanian J, Govindan R. Lung cancer in never smokers: A review. *J Clin Oncol*. 2007;25(5):561-570. doi: 10.1200/JCO.2006.06.8015.

79. Wakelee HA, Chang ET, Gomez SL, et al. Lung cancer incidence in never smokers. *J Clin Oncol*. 2007;25(5):472-478. doi: 10.1200/JCO.2006.07.2983.

80. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers--a different disease. *Nat Rev Cancer*. 2007;7(10):778-790. doi: 10.1038/nrc2190.

81. Spitz MR, Wei Q, Dong Q, Amos CI, Wu X. Genetic susceptibility to lung cancer: The role of DNA damage and repair. *Cancer Epidemiol Biomarkers Prev*. 2003;12(8):689-698.

82. Nguyen ML, Farrell KJ, Gunthel CJ. Non-AIDS-defining malignancies in patients with HIV in the HAART era. *Curr Infect Dis Rep*. 2010;12(1):46-55. doi: 10.1007/s11908-009-0075-6.

83. Matakidou A, Eisen T, Houlston RS. Systematic review of the relationship between family history and lung cancer risk. *Br J Cancer*. 2005;93(7):825-833. doi: 10.1038/sj.bjc.6602769.

84. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. *Am J Respir Crit Care Med*. 2000;161(1):5-8.

85. Buccheri G, Ferrigno D. Lung cancer: Clinical presentation and specialist referral time. *Eur Respir J*. 2004;24(6):898-904. doi: 10.1183/09031936.04.00113603.

86. Koyi H, Hillerdal G, Branden E. Patient's and doctors' delays in the diagnosis of chest tumors. *Lung Cancer*. 2002;35(1):53-57.

87. Corner J, Hopkinson J, Fitzsimmons D, Barclay S, Muers M. Is late diagnosis of lung cancer inevitable? Interview study of patients' recollections of symptoms before diagnosis. *Thorax*. 2005;60(4):314-319. doi: 10.1136/thx.2004.029264.

88. Spiro SG, Gould MK, Colice GL, American College of Chest Physicians. Initial evaluation of the patient with lung cancer: Symptoms, signs, laboratory tests, and paraneoplastic syndromes: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 Suppl):149S-160S. doi: 10.1378/chest.07-1358.

89. Feinstein AR, Wells CK. A clinical-severity staging system for patients with lung cancer. *Medicine (Baltimore)*. 1990;69(1):1-33.

90. Carbone P, Frost J, Feinstein A, Higgins G, Jr., Selawry O. Lung cancer: Perspectives and prospects. *Ann Intern Med*. 1970;73(6):1003-1024.

91. Hooper RG, Tenholder MF, Underwood GH, Beechler CR, Spratling L. Computed tomographic scanning of the brain in initial staging of bronchogenic carcinoma. *Chest*. 1984;85(6):774-776.

92. Thomas K, Gould M. Diagnosis and staging of non-small cell lung cancer. In: Basow D, ed. *UpToDate.* Waltham, MA: UpToDate; 2011.

93. Sculier JP, Chansky K, Crowley JJ, Van Meerbeeck J, Goldstraw P, International Staging Committee and Participating Institutions. The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th edition of the TNM classification of malignant tumors and the proposals for the 7th edition. *J Thorac Oncol*. 2008;3(5):457-466. doi: 10.1097/JTO.0b013e31816de2b8.

94. Kawaguchi T, Takada M, Kubo A, et al. Performance status and smoking status are independent favorable prognostic factors for survival in non-small cell lung cancer: A comprehensive analysis of 26,957 patients with NSCLC. *J Thorac Oncol*. 2010;5(5):620-630. doi: 10.1097/JTO.0b013e3181d2dcd9.

95. Repetto L, Fratino L, Audisio RA, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: An Italian group for Geriatric Oncology Study. *J Clin Oncol*. 2002;20(2):494-502.

96. Hurria A, Cohen H. Comprehensive geriatric assessment for patients with cancer. In: Basow D, ed. *UpToDate.* Waltham, MA: UpToDate; 2011.

97. Hurria A, Lichtman SM, Gardes J, et al. Identifying vulnerable older adults with cancer: Integrating geriatric assessment into oncology practice. *J Am Geriatr Soc*. 2007;55(10):1604-1608. doi: 10.1111/j.1532-5415.2007.01367.x.

98. Hurria A, Cirrincione CT, Muss HB, et al. Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401. *J Clin Oncol*. 2011;29(10):1290-1296. doi: 10.1200/JCO.2010.30.6985.

99. West H, Valleries E, Schild S. Management of stage I and stage II non-small cell lung cancer. In: Basow D, ed. *UpToDate.* Waltham, MA: UpToDate; 2011.

100. Heffner J. Management of malignant pleural effusions. In: Basow D, ed. *UpToDate.* Waltham, MA: UpToDate; 2011.

101. Hu C, Chang EL, Hassenbusch SJ,3rd, et al. Nonsmall cell lung cancer presenting with synchronous solitary brain metastasis. *Cancer*. 2006;106(9):1998-2004. doi: 10.1002/cncr.21818.

102. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med*. 1990;322(8):494-500. doi: 10.1056/NEJM199002223220802.

103. Burt M, Wronski M, Arbit E, Galicich JH. Resection of brain metastases from non-small-cell lung carcinoma. results of therapy. memorial sloan-kettering cancer center thoracic surgical staff. *J Thorac Cardiovasc Surg*. 1992;103(3):399-410; discussion 410-1.

104. Marko NF, Suh JH, Chao ST, et al. Gamma knife stereotactic radiosurgery for the management of incidentally-identified brain metastasis from non-small cell lung cancer. *J Neurooncol*. 2011;104(3):817-824. doi: 10.1007/s11060-011-0553-1.

105. Ricciardi S, de Marinis F. Multimodality management of non-small cell lung cancer patients with brain metastases. *Curr Opin Oncol*. 2010;22(2):86-93. doi: 10.1097/CCO.0b013e3283350106.

106. Zabel A, Debus J. Treatment of brain metastases from non-small-cell lung cancer (NSCLC): Radiotherapy. *Lung Cancer*. 2004;45 Suppl 2:S247-52. doi: 10.1016/j.lungcan.2004.07.968.

107. Alexander E,3rd, Moriarty TM, Davis RB, et al. Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. *J Natl Cancer Inst*. 1995;87(1):34-40.

108. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys*. 1999;45(2):427-434.

109. Marko NF, Weil RJ. Radiotherapy: Neurocognitive considerations in the treatment of brain metastases. *Nat Rev Clin Oncol*. 2010;7(4):185-186. doi: 10.1038/nrclinonc.2010.30.

110. Wagner H,Jr. Just enough palliation: Radiation dose and outcome in patients with non-small-cell lung cancer. *J Clin Oncol*. 2008;26(24):3920-3922. doi: 10.1200/JCO.2008.17.3674.

111. Fairchild A, Harris K, Barnes E, et al. Palliative thoracic radiotherapy for lung cancer: A systematic review. *J Clin Oncol*. 2008;26(24):4001-4011. doi: 10.1200/JCO.2007.15.3312.

112. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: A population-based time-trend analysis. *J Clin Oncol*. 2010;28(35):5153-5159. doi: 10.1200/JCO.2010.30.0731.

113. Delbaldo C, Michiels S, Syz N, Soria JC, Le Chevalier T, Pignon JP. Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: A meta-analysis. *JAMA*. 2004;292(4):470-484. doi: 10.1001/jama.292.4.470.

114. Alberola V, Camps C, Provencio M, et al. Cisplatin plus gemcitabine versus a cisplatin-based triplet versus nonplatinum sequential doublets in advanced non-small-cell lung cancer:

A Spanish Lung Cancer Group phase III randomized trial. *J Clin Oncol*. 2003;21(17):3207-3213. doi: 10.1200/JCO.2003.12.038.

115. Comella P, Filippelli G, De Cataldis G, et al. Efficacy of the combination of cisplatin with either gemcitabine and vinorelbine or gemcitabine and paclitaxel in the treatment of locally advanced or metastatic non-small-cell lung cancer: A phase III randomised trial of the Southern Italy Cooperative Oncology Group (SICOG 0101). *Ann Oncol*. 2007;18(2):324-330. doi: 10.1093/annonc/mdl396.

116. Greco FA, Spigel DR, Kuzur ME, et al. Paclitaxel/carboplatin/gemcitabine versus gemcitabine/vinorelbine in advanced non-small-cell lung cancer: A phase II/III study of the Minnie Pearl Cancer Research Network. *Clin Lung Cancer*. 2007;8(8):483-487. doi: 10.3816/CLC.2007.n.032.

117. Socinski MA, Baggstrom MQ, Hensing TA. Duration of therapy in advanced, metastatic non-small-cell lung cancer. *Clin Adv Hematol Oncol*. 2003;1(1):33-38.

118. Socinski MA, Schell MJ, Peterman A, et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. *J Clin Oncol*. 2002;20(5):1335-1343.

119. von Plessen C, Bergman B, Andresen O, et al. Palliative chemotherapy beyond three courses conveys no survival or consistent quality-of-life benefits in advanced non-small-cell lung cancer. *Br J Cancer*. 2006;95(8):966-973. doi: 10.1038/sj.bjc.6603383.

120. Park JO, Kim SW, Ahn JS, et al. Phase III trial of two versus four additional cycles in patients who are nonprogressive after two cycles of platinum-based chemotherapy in non small-cell lung cancer. *J Clin Oncol*. 2007;25(33):5233-5239. doi: 10.1200/JCO.2007.10.8134.

121. Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: An individual patient data meta-analysis. *J Natl Cancer Inst*. 2007;99(11):847-857. doi: 10.1093/jnci/djk196.

122. Lilenbaum R. Initial systemic chemotherapy for advanced non-small cell lung cancer. In: Basow D, ed. *UpToDate.* Waltham, MA: UpToDate; 2011.

123. D'Addario G, Pintilie M, Leighl NB, Feld R, Cerny T, Shepherd FA. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: A meta-analysis of the published literature. *J Clin Oncol*. 2005;23(13):2926-2936. doi: 10.1200/JCO.2005.03.045.

124. Hainsworth JD, Spigel DR, Farley C, et al. Weekly docetaxel versus docetaxel/gemcitabine in the treatment of elderly or poor performance status patients with advanced nonsmall cell lung cancer: A randomized phase 3 trial of the Minnie Pearl Cancer Research Network. *Cancer*. 2007;110(9):2027-2034. doi: 10.1002/cncr.23019.

125. Langer CJ, O'Byrne KJ, Socinski MA, et al. Phase III trial comparing paclitaxel poliglumex (CT-2103, PPX) in combination with carboplatin versus standard paclitaxel and

carboplatin in the treatment of PS 2 patients with chemotherapy-naive advanced non-small cell lung cancer. *J Thorac Oncol*. 2008;3(6):623-630. doi: 10.1097/JTO.0b013e3181753b4b.

126. Lilenbaum RC, Herndon JE,2nd, List MA, et al. Single-agent versus combination chemotherapy in advanced non-small-cell lung cancer: The Cancer and Leukemia Group B (study 9730). *J Clin Oncol*. 2005;23(1):190-196. doi: 10.1200/JCO.2005.07.172.

127. Belani CP, Fossella F. Elderly subgroup analysis of a randomized phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for first-line treatment of advanced nonsmall cell lung carcinoma (TAX 326). *Cancer*. 2005;104(12):2766-2774. doi: 10.1002/cncr.21495.

128. Quoix E, Zalcman G, Oster JP, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. *Lancet*. 2011;378(9796):1079-1088. doi: 10.1016/S0140-6736(11)60780-0.

129. Syrigos KN, Vansteenkiste J, Parikh P, et al. Prognostic and predictive factors in a randomized phase III trial comparing cisplatin-pemetrexed versus cisplatin-gemcitabine in advanced non-small-cell lung cancer. *Ann Oncol*. 2010;21(3):556-561. doi: 10.1093/annonc/mdp392.

130. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: A review of two phase III studies. *Oncologist*. 2009;14(3):253-263. doi: 10.1634/theoncologist.2008-0232.

131. Weiss GJ, Langer C, Rosell R, et al. Elderly patients benefit from second-line cytotoxic chemotherapy: A subset analysis of a randomized phase III trial of pemetrexed compared with docetaxel in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol*. 2006;24(27):4405-4411. doi: 10.1200/JCO.2006.06.7835.

132. Di Maio M, Chiodini P, Georgoulias V, et al. Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol*. 2009;27(11):1836-1843. doi: 10.1200/JCO.2008.17.5844.

133. Massarelli E, Andre F, Liu DD, et al. A retrospective analysis of the outcome of patients who have received two prior chemotherapy regimens including platinum and docetaxel for recurrent non-small-cell lung cancer. *Lung Cancer*. 2003;39(1):55-61.

134. Dvorak HF. Vascular permeability factor/vascular endothelial growth factor: A critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. *J Clin Oncol*. 2002;20(21):4368-4380.

135. Carmeliet P. Angiogenesis in life, disease and medicine. *Nature*. 2005;438(7070):932-936. doi: 10.1038/nature04478.

136. Gerber HP, Ferrara N. Pharmacology and pharmacodynamics of bevacizumab as monotherapy or in combination with cytotoxic therapy in preclinical studies. *Cancer Res*. 2005;65(3):671-680.

137. Sandler A, Yi J, Dahlberg S, et al. Treatment outcomes by tumor histology in Eastern Cooperative Group study E4599 of bevacizumab with paclitaxel/carboplatin for advanced non-small cell lung cancer. *J Thorac Oncol*. 2010;5(9):1416-1423. doi: 10.1097/JTO.0b013e3181da36f4.

138. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: Results from a randomised phase III trial (AVAiL). *Ann Oncol*. 2010;21(9):1804-1809. doi: 10.1093/annonc/mdq020.

139. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. *J Clin Oncol*. 2009;27(8):1227-1234. doi: 10.1200/JCO.2007.14.5466.

140. William WN,Jr, Kies MS, Fossella FV, et al. Phase 2 study of carboplatin, docetaxel, and bevacizumab as frontline treatment for advanced nonsmall-cell lung cancer. *Cancer*. 2010;116(10):2401-2408. doi: 10.1002/cncr.24996.

141. Clement-Duchene C, Krupitskaya Y, Ganjoo K, et al. A phase II first-line study of gemcitabine, carboplatin, and bevacizumab in advanced stage nonsquamous non-small cell lung cancer. *J Thorac Oncol*. 2010;5(11):1821-1825. doi: 10.1097/JTO.0b013e3181f1d23c.

142. Patel JD, Hensing TA, Rademaker A, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2009;27(20):3284-3289. doi: 10.1200/JCO.2008.20.8181.

143. Heist RS, Fidias P, Huberman M, et al. A phase II study of oxaliplatin, pemetrexed, and bevacizumab in previously treated advanced non-small cell lung cancer. *J Thorac Oncol*. 2008;3(10):1153-1158. doi: 10.1097/JTO.0b013e318187273f.

144. Lilenbaum R, Raez L, Tseng J, Seigel L, Davila E. Efficacy and safety of oxaliplatin and gemcitabine with bevacizumab in advanced non-small cell lung cancer. *J Thorac Oncol*. 2008;3(5):511-515. doi: 10.1097/JTO.0b013e31816de28f.

145. Zinner RG, Saxman SB, Peng G, Monberg MJ, Ortuzar WI. Treatment rationale and study design for a randomized trial of pemetrexed/carboplatin followed by maintenance pemetrexed versus paclitaxel/carboplatin/bevacizumab followed by maintenance bevacizumab in patients with advanced non-small-cell lung cancer of nonsquamous histology. *Clin Lung Cancer*. 2010;11(5):352-357. doi: 10.3816/CLC.2010.n.045.

146. Dillman RO, Zusman DR, McClure SE. Surgical resection and long-term survival for octogenarians who undergo surgery for non-small-cell lung cancer. *Clin Lung Cancer*. 2009;10(2):130-134. doi: 10.3816/CLC.2009.n.017.

147. Sigel K, Bonomi M, Packer S, Wisnivesky J. Effect of age on survival of clinical stage I non-small-cell lung cancer. *Ann Surg Oncol*. 2009;16(7):1912-1917. doi: 10.1245/s10434-009-0475-8.

148. Owonikoko TK, Ragin CC, Belani CP, et al. Lung cancer in elderly patients: An analysis of the Surveillance, Epidemiology, and End Results database. *J Clin Oncol*. 2007;25(35):5570-5577. doi: 10.1200/JCO.2007.12.5435.

149. Ramsey SD, Howlader N, Etzioni RD, Donato B. Chemotherapy use, outcomes, and costs for older persons with advanced non-small-cell lung cancer: Evidence from Surveillance, Epidemiology and End Results-medicare. *J Clin Oncol*. 2004;22(24):4971-4978. doi: 10.1200/JCO.2004.05.031.

150. Rasco DW, Yan J, Xie Y, Dowell JE, Gerber DE. Looking beyond Surveillance, Epidemiology, and End results: Patterns of chemotherapy administration for advanced non-small cell lung cancer in a contemporary, diverse population. *J Thorac Oncol*. 2010;5(10):1529-1535. doi: 10.1097/JTO.0b013e3181e9a00f; 10.1097/JTO.0b013e3181e9a00f.

151. Chrischilles EA, Pendergast JF, Kahn KL, et al. Adverse events among the elderly receiving chemotherapy for advanced non-small-cell lung cancer. *J Clin Oncol*. 2010;28(4):620-627. doi: 10.1200/JCO.2009.23.8485.

152. Arias E. United States life tables, 2006. *Natl Vital Stat Rep*. 2010;58(21):1-40.

153. Pepe C, Hasan B, Winton TL, et al. Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. *J Clin Oncol*. 2007;25(12):1553-1561. doi: 10.1200/JCO.2006.09.5570.

154. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. the elderly lung cancer vinorelbine italian study group. *J Natl Cancer Inst*. 1999;91(1):66-72.

155. Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: The Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst*. 2003;95(5):362-372.

156. Langer CJ, Manola J, Bernardo P, et al. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: Implications of Eastern Cooperative Oncology Group 5592, a randomized trial. *J Natl Cancer Inst*. 2002;94(3):173-181.

157. Hensing TA, Peterman AH, Schell MJ, Lee JH, Socinski MA. The impact of age on toxicity, response rate, quality of life, and survival in patients with advanced, stage IIIB or IV nonsmall cell lung carcinoma treated with carboplatin and paclitaxel. *Cancer*. 2003;98(4):779-788. doi: 10.1002/cncr.11548.

158. Blanchard EM, Moon J, Hesketh PJ, et al. Comparison of platinum-based chemotherapy in patients older and younger than 70 years: An analysis of Southwest Oncology Group trials 9308 and 9509. *J Thorac Oncol*. 2011;6(1):115-120. doi: 10.1097/JTO.0b013e3181fbebfd.

159. Earle CC, Tsai JS, Gelber RD, Weinstein MC, Neumann PJ, Weeks JC. Effectiveness of chemotherapy for advanced lung cancer in the elderly: Instrumental variable and propensity analysis. *J Clin Oncol*. 2001;19(4):1064-1070.

160. Hardy D, Liu CC, Cormier JN, Xia R, Du XL. Cardiac toxicity in association with chemotherapy and radiation therapy in a large cohort of older patients with non-small-cell lung cancer. *Ann Oncol*. 2010;21(9):1825-1833. doi: 10.1093/annonc/mdq042.

161. Lathan CS, Neville BA, Earle CC. The effect of race on invasive staging and surgery in non-small-cell lung cancer. *J Clin Oncol*. 2006;24(3):413-418. doi: 10.1200/JCO.2005.02.1758.

162. Suga JM, Nguyen DV, Mohammed SM, et al. Racial disparities on the use of invasive and noninvasive staging in patients with non-small cell lung cancer. *J Thorac Oncol*. 2010;5(11):1772-1778. doi: 10.1097/JTO.0b013e3181f69f22.

163. Esnaola NF, Gebregziabher M, Knott K, et al. Underuse of surgical resection for localized, non-small cell lung cancer among whites and African Americans in South Carolina. *Ann Thorac Surg*. 2008;86(1):220-6; discussion 227. doi: 10.1016/j.athoracsur.2008.02.072.

164. Ou SH, Zell JA, Ziogas A, Anton-Culver H. Low socioeconomic status is a poor prognostic factor for survival in stage I nonsmall cell lung cancer and is independent of surgical treatment, race, and marital status. *Cancer*. 2008;112(9):2011-2020. doi: 10.1002/cncr.23397.

165. Potosky AL, Saxman S, Wallace RB, Lynch CF. Population variations in the initial treatment of non-small-cell lung cancer. *J Clin Oncol*. 2004;22(16):3261-3268. doi: 10.1200/JCO.2004.02.051.

166. Hayman JA, Abrahamse PH, Lakhani I, Earle CC, Katz SJ. Use of palliative radiotherapy among patients with metastatic non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2007;69(4):1001-1007. doi: 10.1016/j.ijrobp.2007.04.059.

167. Lang K, Marciniak MD, Faries D, et al. Trends and predictors of first-line chemotherapy use among elderly patients with advanced non-small cell lung cancer in the United States. *Lung Cancer*. 2009;63(2):264-270. doi: 10.1016/j.lungcan.2008.05.003.

168. Hardy D, Cormier JN, Xing Y, Liu CC, Xia R, Du XL. Chemotherapy-associated toxicity in a large cohort of elderly patients with non-small cell lung cancer. *J Thorac Oncol*. 2010;5(1):90-98. doi: 10.1097/JTO.0b013e3181c0a128.

169. Halpern MT, Ward EM, Pavluck AL, Schrag NM, Bian J, Chen AY. Association of insurance status and ethnicity with cancer stage at diagnosis for 12 cancer sites: A retrospective analysis. *Lancet Oncol*. 2008;9(3):222-231. doi: 10.1016/S1470-2045(08)70032-9.

170. Andersen R. *A behavior model of families' use of health services.* Chicago, IL: Center for Health Administration Studies, University of Chicago; 1968.

171. Andersen RM. National health surveys and the behavioral model of health services use. *Med Care*. 2008;46(7):647-653. doi: 10.1097/MLR.0b013e31817a835d.

172. Andersen RM. Revisiting the behavioral model and access to medical care: Does it matter? *J Health Soc Behav*. 1995;36(1):1-10.

173. Aday LA, Begley CE, Lairson DR, Balkrishnan R. *Evaluating the healthcare system: Effectiveness, efficiency, and equity.* 3rd ed. Chicago, IL: Health Administration Press; 2004.

174. Andersen R, Davidson P. Improving access to care in America: Individual and contextual indicators. In: Andersen R, Rice T, Kominski G, eds. *Changing the U.S. health care system: Key issues in health services policy and management.* 3rd ed. San Francisco, CA: Jossey-Bass; 2007:3-31.

175. Brown JS, Eraut D, Trask C, Davison AG. Age and the treatment of lung cancer. *Thorax*. 1996;51(6):564-568.

176. Agarwal M, Brahmanday G, Chmielewski GW, Welsh RJ, Ravikrishnan KP. Age, tumor size, type of surgery, and gender predict survival in early stage (stage I and II) non-small cell lung cancer after surgical resection. *Lung Cancer*. 2010;68(3):398-402. doi: 10.1016/j.lungcan.2009.08.008.

177. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Survival determinants in extensive-stage non-small-cell lung cancer: The Southwest Oncology Group experience. *J Clin Oncol*. 1991;9(9):1618-1626.

178. Mandrekar SJ, Northfelt DW, Schild SE, et al. Impact of pretreatment factors on adverse events: A pooled analysis of North Central Cancer Treatment Group advanced stage non-small cell lung cancer trials. *J Thorac Oncol*. 2006;1(6):556-563.

179. Brahmer JR, Dahlberg SE, Gray RJ, et al. Sex differences in outcome with bevacizumab therapy: Analysis of patients with advanced-stage non-small cell lung cancer treated with or without bevacizumab in combination with paclitaxel and carboplatin in the Eastern Cooperative Oncology Group trial 4599. *J Thorac Oncol*. 2011;6(1):103-108. doi: 10.1097/JTO.0b013e3181fa8efd.

180. Ferguson MK, Wang J, Hoffman PC, et al. Sex-associated differences in survival of patients undergoing resection for lung cancer. *Ann Thorac Surg*. 2000;69(1):245-9; discussion 249-50.

181. Fu JB, Kau TY, Severson RK, Kalemkerian GP. Lung cancer in women: Analysis of the national Surveillance, Epidemiology, and End Results database. *Chest*. 2005;127(3):768-777. doi: 10.1378/chest.127.3.768.

182. Ferguson MK, Skosey C, Hoffman PC, Golomb HM. Sex-associated differences in presentation and survival in patients with lung cancer. *J Clin Oncol*. 1990;8(8):1402-1407.

183. Wakelee HA, Wang W, Schiller JH, et al. Survival differences by sex for patients with advanced non-small cell lung cancer on Eastern Cooperative Oncology Group trial 1594. *J Thorac Oncol*. 2006;1(5):441-446.

184. Siddiqui F, Bae K, Langer CJ, et al. The influence of gender, race, and marital status on survival in lung cancer patients: Analysis of radiation therapy oncology group trials. *J Thorac Oncol*. 2010;5(5):631-639.

185. Jatoi A, Novotny P, Cassivi S, et al. Does marital status impact survival and quality of life in patients with non-small cell lung cancer? observations from the Mayo Clinic lung cancer cohort. *Oncologist*. 2007;12(12):1456-1463. doi: 10.1634/theoncologist.12-12-1456.

186. Du XL, Lin CC, Johnson NJ, Altekruse S. Effects of individual-level socioeconomic factors on racial disparities in cancer treatment and survival: Findings from the national longitudinal mortality study, 1979-2003. *Cancer*. 2011;117(14):3242-3251. doi: 10.1002/cncr.25854; 10.1002/cncr.25854.

187. Shugarman LR, Sorbero ME, Tian H, Jain AK, Ashwood JS. An exploration of urban and rural differences in lung cancer survival among Medicare beneficiaries. *Am J Public Health*. 2008;98(7):1280-1287. doi: 10.2105/AJPH.2006.099416.

188. Sandler A, Yi J, Dahlberg S, et al. Treatment outcomes by tumor histology in Eastern Cooperative Group study E4599 of bevacizumab with paclitaxel/carboplatin for advanced non-small cell lung cancer. *J Thorac Oncol*. 2010;5(9):1416-1423. doi: 10.1097/JTO.0b013e3181da36f4.

189. Surveillance Research Program, National Cancer Institute. Overview of the SEER program. http://seer.cancer.gov/about/overview.html. Accessed April, 26, 2011.

190. Safran DG, Neuman P, Schoen C, et al. Prescription drug coverage and seniors: Findings from a 2003 national survey. *Health Aff (Millwood)*. 2005;Suppl Web Exclusives:W5-152-W5-166. doi: 10.1377/hlthaff.w5.152.

191. Henry J. Kaiser Family Foundation. The Medicare prescription drug benefit: An updated fact sheet. http://http://www.kff.org/medicare/upload/7044-13.pdf. Updated 2012. Accessed November, 14, 2012.

192. Surveillance Research Program, National Cancer Institute. SEER-Medicare: Brief description of the SEER-medicare database. http://healthservices.cancer.gov/seermedicare/overview/. Accessed May 2, 2011.

193. Obeidat NA, Pradel FG, Zuckerman IH, DeLisle S, Mullins CD. Outcomes of irinotecan-based chemotherapy regimens in elderly Medicare patients with metastatic colorectal cancer. *Am J Geriatr Pharmacother*. 2009;7(6):343-354. doi: 10.1016/j.amjopharm.2009.11.005.

194. Mullins CD, Onukwugha E, Bikov K, Seal B, Hussain A. Health disparities in staging of SEER-Medicare prostate cancer patients in the United States. *Urology*. 2010;76(3):566-572. doi: 10.1016/j.urology.2009.10.061.

195. Bach PB, Guadagnoli E, Schrag D, Schussler N, Warren JL. Patient demographic and socioeconomic characteristics in the SEER-Medicare database applications and limitations. *Med Care*. 2002;40(8 Suppl):IV-19-25. doi: 10.1097/01.MLR.0000020934.40692.C0.

196. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: Content, research applications, and generalizability to the United States elderly population. *Med Care*. 2002;40(8 Suppl):IV-3-18. doi: 10.1097/01.MLR.0000020942.47004.03.

197. *Avastin [package insert]*. South San Francisco, CA: Genentech; 2011.

198. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis*. 1987;40(5):373-383.

199. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.

200. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: Differing perspectives. *J Clin Epidemiol*. 1993;46(10):1075-9; discussion 1081-90.

201. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. *J Clin Epidemiol*. 2000;53(12):1258-1267.

202. Klabunde CN, Harlan LC, Warren JL. Data sources for measuring comorbidity: A comparison of hospital records and Medicare claims for cancer patients. *Med Care*. 2006;44(10):921-928. doi: 10.1097/01.mlr.0000223480.52713.b9.

203. Klabunde CN, Legler JM, Warren JL, Baldwin LM, Schrag D. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. *Ann Epidemiol*. 2007;17(8):584-590. doi: 10.1016/j.annepidem.2007.03.011.

204. Baldwin LM, Klabunde CN, Green P, Barlow W, Wright G. In search of the perfect comorbidity measure for use with administrative claims data: Does it exist? *Med Care*. 2006;44(8):745-753. doi: 10.1097/01.mlr.0000223475.70440.07.

205. Surveillance Research Program, National Cancer Institute. SEER-Medicare: Calculation of comorbidity weights. http://healthservices.cancer.gov/seermedicare/program/comorbidity.html. Accessed July 3, 2011.

206. Ranpura V, Hapani S, Chuang J, Wu S. Risk of cardiac ischemia and arterial thromboembolic events with the angiogenesis inhibitor bevacizumab in cancer patients: A meta-analysis of randomized controlled trials. *Acta Oncol*. 2010;49(3):287-297. doi: 10.3109/02841860903524396.

207. Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly advanced stage non-small cell lung cancer (NSCLC) patients (pts) treatedwith bevacizumab (B) in

combination with carboplatin (C) and paclitaxel(P): Analysis of Eastern Cooperative Oncology Group (ECOG) 4599 study. *J Clin Oncol*. 2007;25(18 suppl):393S.

208. Sandler AB, Gray R, Brahmer J, et al. Randomized phase II/III trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC # 704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) trial - E4599. *J Clin Oncol*. 2005;23(16 suppl):LBA4.

209. Ettinger D, Johnson B. Update: NCCN small cell and non-small cell lung cancer clinical practice guidelines. *J Natl Compr Canc Netw*. 2005;3 Suppl 1:S17-21.

210. Thornton AD, Ravn P, Winslet M, Chester K. Angiogenesis inhibition with bevacizumab and the surgical management of colorectal cancer. *Br J Surg*. 2006;93(12):1456-1463. doi: 10.1002/bjs.5624.

211. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group study E3200. *J Clin Oncol*. 2007;25(12):1539-1544. doi: 10.1200/JCO.2006.09.6305.

212. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350(23):2335-2342. doi: 10.1056/NEJMoa032691.

213. Kabbinavar FF, Flynn PJ, Kozloff M, et al. Gastrointestinal perforation associated with bevacizumab use in metastatic colorectal cancer: Results from a large treatment observational cohort study. *Eur J Cancer*. 2012;48(8):1126-1132. doi: 10.1016/j.ejca.2012.02.052.

214. Meyerhardt JA, Li L, Sanoff HK, Carpenter W,4th, Schrag D. Effectiveness of bevacizumab with first-line combination chemotherapy for Medicare patients with stage IV colorectal cancer. *J Clin Oncol*. 2012;30(6):608-615. doi: 10.1200/JCO.2011.38.9650.

215. Goulart B, Ramsey S. A trial-based assessment of the cost-utility of bevacizumab and chemotherapy versus chemotherapy alone for advanced non-small cell lung cancer. *Value Health*. 2011;14(6):836-845. doi: 10.1016/j.jval.2011.04.004.

216. Hoang T, Dahlberg SE, Sandler AB, Brahmer JR, Schiller JH, Johnson DH. Prognostic models to predict survival in non-small-cell lung cancer patients treated with first-line paclitaxel and carboplatin with or without bevacizumab. *J Thorac Oncol*. 2012;7(9):1361-1368. doi: 10.1097/JTO.0b013e318260e106; 10.1097/JTO.0b013e318260e106.

217. Surveillance Research Program, National Cancer Institute. Health Service Areas (HSAs). http://seer.cancer.gov/seerstat/variables/countyattribs/hsa.html. Accessed May 3, 2012.