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**Treatment Patterns and Healthcare Resource Utilization and Payments in
Patients with Lung Cancer in the Texas Medicaid Program**

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Patients with Lung Cancer in the Texas Medicaid Program**

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Abstract

Treatment Patterns and Healthcare Resource Utilization and Payments in Patients with Lung Cancer in the Texas Medicaid Program

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The economic burden associated with the treatment of lung cancer is substantial. With the introduction of targeted therapy and immunotherapy, treatment options for lung cancer management have expanded in recent years. However, little is known about treatment patterns and healthcare utilization and payments for lung cancer patients enrolled in the Texas Medicaid program.

The objective of this study was to evaluate treatment patterns and healthcare resource utilization and payments for lung cancer patients enrolled in Texas Medicaid. A total of 453 newly diagnosed lung cancer patients were identified between 2004 and 2021. There were significant differences in proportions of patients receiving chemotherapy, targeted therapy, and immunotherapy by treatment line ($p < 0.0001$). Chemotherapy was the most frequently prescribed first-line treatment for enrollees with lung cancer (363, 80.1%). Immunotherapy (53, 11.7%), the second most used first-line treatment, exceeded targeted therapy (37, 8.2%). Only one-third (146) of patients received subsequent-line treatment, in which immunotherapy increased greatly.

Platinum-based doublets were the main first-line treatment while single-agent chemotherapy dominated in subsequent line.

Office visits (mean=19.5) and outpatient visits (mean=13.6) accounted for the majority of healthcare resource utilization during the 1-year follow-up period. Compared to the chemotherapy group, immunotherapy had a significantly higher number of office visits while targeted therapy had a significantly lower number of office visits. Targeted therapy also had a significantly lower number of ED visits. Consistent with healthcare resources utilization, payments associated with office visits and outpatient visits were primary drivers of payments. Compared to the chemotherapy group, the immunotherapy group had 160.93% higher total payments ($p<0.0001$), while the targeted therapy group had 29.99% lower total payments ($p=0.1818$).

Findings from our study showed that although chemotherapy was still the mainstream treatment for lung cancer, the treatment landscape has shifted to immunotherapy. This could be attributed to a decreased utilization of chemotherapy and increased utilization of immunotherapy in subsequent-line treatment. Meanwhile, the greater use of immunotherapy might be a driving factor for more outpatient visits and office visits associated with higher payments. Future studies of real-world use of immunotherapy are needed to better understand the economic burden.

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Chapter 1 Literature Review

1.1 Chapter overview

This chapter provides an overview of lung cancer, including its main subtypes, symptoms, screening, staging and performance status, and epidemiology. Treatment is discussed with a focus on systemic chemotherapy, targeted therapy, and immunotherapy for non-small cell lung cancer (NSCLC) since it accounts for 85% of lung cancer cases and the treatment options for small cell lung cancer (SCLC) and NSCLC are similar. Additionally, published studies regarding lung cancer treatment patterns, treatment outcomes, and lung cancer-related healthcare utilization and costs are summarized. Lastly, the study rationale and objectives are provided at the end of this chapter.

1.2 Overview of lung cancer

Lung cancer originates in the lung, and as the disease progresses, cancer cells may spread to lymph nodes or other organs in the body. The two main types of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). As their names imply, NSCLC cells are larger in size than SCLC cells. Compared to NSCLC, SCLC is more aggressive and spreads more rapidly. NSCLC is more common, accounting for 85% to 90% of lung cancer cases in the United States. [1] [2] [3] There are diverse subtypes of NSCLC defined by pathological characteristics. The three predominant subtypes of NSCLC are adenocarcinoma (AdCa), squamous cell (epidermoid) carcinoma (SqCC), and large cell (undifferentiated) carcinoma. Adenocarcinoma starts in the distal airway and accounts for about 40% of lung cancer cases, while squamous cell carcinoma arises in the inner airway and affects 20% to 30% of lung cancer patients. [4] In contrast to the other two subtypes of NSCLC, large cell carcinoma represents only 10% to 15% of lung cancer cases and appears in all parts of the lung. Its disease progression and metastasis are

relatively fast. Other less frequent subtypes of NSCLC include adenosquamous carcinoma and sarcomatoid carcinoma.

The common symptoms of lung cancer include persistent coughing, hoarseness of voice, blood or rust-colored sputum, shortness of breath, chest pain, weight loss, and infections such as bronchitis and pneumonia. [5] [6] [7] However, these symptoms are usually ignored because patients tend to think of them as common respiratory conditions until lung cancer progresses to a serious condition. Thus, most patients with lung cancer are diagnosed in an advanced disease stage with metastasis. [8, 5] With disease progression, more symptoms are likely to appear. If the cancer metastasizes to the brain or the spinal cord, patients will experience loss of balance, weakness or numbness of arms and legs, headache, and seizures. If the cancer metastasizes to the liver, patients may have yellow skin and eyes. Lung cancer may cause syndromes as well, such as Horner syndrome, superior vena cava syndrome, and paraneoplastic syndromes.

Screening is an important way to detect lung cancer in an early stage. However, the risks and benefits of screening are still under debate. [9, 10, 11, 12, 13] Screening can help to identify patients at an early disease stage, but may also result in over-diagnosis and harm from exposure to radiation. The National Lung Screening Trial (NLST) provided encouraging evidence that a low-dose computed tomography (CT) scan used for screening could reduce the risk of dying from lung cancer by 20%. [11] Based on that study, The American Cancer Society (ACS) recommends lung cancer screening for people who are: (1) 55 to 74 years old; (2) former (quit smoking within 15 years) or current smokers; (3) have at least a 30 pack-year smoking history; or (4) in fair health. [12] Since 2015, the expense of annual lung screening for people with a high risk of lung cancer has been covered by Medicare. [14] Based on screening results and symptoms, physicians may order further exams and tests including sputum cytology, chest x-ray, CT scan, and biopsy.

1.3 Staging and performance status

1.3.1 Staging

Treatment for lung cancer depends on lung cancer type, disease stage, and patients' performance status (PS). Disease stage describes the extent of deterioration of the patient's condition related to cancer. In general, NSCLC is staged according to the tumor node metastasis (TNM) system developed collaboratively by the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC).(Table 1.1) [7] [15] The TNM system is the most useful clinical staging system because it synthesizes assessment of size and extent of the primary tumor (T), presence of regional lymph node involvement (N), and status of distant metastases (M). The definitions related to elements of the TNM system are summarized in Table 1.2. For SCLC, classification consists of two stages according to The Veterans' Administration Lung Study Group (VALSG) two-stage classification scheme: limited-stage and extensive-stage. [16] According to VALSG, "the limited-stage (LS) is defined as: (a) disease confined to one hemithorax, although local extension may be present; (b) no extrathoracic metastases except for ipsilateral supraclavicular lymph nodes if they can be included in the same radiation port as the primary tumor; and (c) primary tumor and regional nodes that can be adequately encompassed in a radiation port. Extensive-stage (ES) disease is defined as disease that cannot be classified as limited, including malignant pleural or pericardial effusions, contralateral hilar or supraclavicular lymph nodes, and hematogenous metastases."

Table 1.1. Anatomic stage/prognostic groups according to AJCC system^a

Stage		T	N	M
Occult Carcinoma		TX	N0	M0
Stage 0		Tis	N0	M0
Stage I	IA1	T1mi	N0	M0
		T1a	N0	M0
	IA2	T1b	N0	M0
	IA3	T1c	N0	M0
	IB	T2a	N0	M0
Stage II	IIA	T2b	N0	M0
	IIB	T1a	N1	M0
		T1b	N1	M0
		T1c	N1	M0
		T2a	N1	M0
		T2b	N1	M0
		T3	N0	M0
Stage III	IIIA	T1a	N2	M0
		T1b	N2	M0
		T1c	N2	M0
		T2a	N2	M0
		T2b	N2	M0
		T3	N1	M0
		T4	N0	M0
		T4	N1	M0
	IIIB	T1a	N3	M0
		T1b	N3	M0
		T1c	N3	M0
		T2a	N3	M0
		T2b	N3	M0
		T3	N2	M0
		T4	N2	M0
	IIIC	T3	N3	M0
		T4	N3	M0
Stage IV	IVA	Any T	Any N	M1a
		Any T	Any N	M1b
	IVB	Any T	Any N	M1c

^a Elements of the TNM system are defined in Table 1.2.

Source: Amin MB, AJCC Cancer Staging Manual, American Joint Committee on Cancer; American Cancer Society, 2017. Accessed at <https://cancerstaging.org>, November 2021.

Table 1.2. Definitions of TNM elements

Primary Tumor (T)	Element Definition
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ Squamous cell carcinoma in situ (SCIS) Adenocarcinoma in situ (AIS): adenocarcinoma with pure lepidic pattern, <3 cm in greatest dimension
T1	Tumor <3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus) ¹
T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (< 3 cm in greatest dimension) with a predominantly lepidic pattern and <5 mm invasion in greatest dimension
T1a	Tumor <1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T 1a, but these tumors are uncommon
T1b	Tumor >1 cm but < 2 cm in greatest dimension
T1c	Tumor >2 cm but < 3 cm in greatest dimension
T2	Tum or >3 cm but <5 cm or having any of the following features: • Involves the main bronchus regardless of distance to the carina, but without involvement of the carina • Invades visceral pleura (PL1 or PL2) • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung T2 tumors with these features are classified as T2a if < 4 cm or if the size cannot be determined and T2b if >4 cm but <5 cm
T2a	Tumor >3 cm but < 4 cm in greatest dimension
T2b	Tumor >4 cm but < 5 cm in greatest dimension
T3	Tumor >5 cm but <7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary tumor
T4	Tumor >7 cm or tum or of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tum or nodule(s) in an ipsilateral lobe different from that of the primary tumor

Regional Lymph Nodes (N)	Element Definition
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant Metastasis (M)	Element Definition
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tum or nodule(s) in a contralateral lobe; tum or with pleural or pericardial nodules or malignant pleural or pericardial effusion. Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor. ²
M1b	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
M1c	Multiple extrathoracic metastases in a single organ or in multiple organs

Notes: 1. The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

2. Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

Source: Amin MB, AJCC Cancer Staging Manual, American Joint Committee on Cancer; American Cancer Society, 2017. Accessed at <https://cancerstaging.org>, November 2021.

1.3.2 Performance status

Performance status (PS) is a standard criterion measuring how lung cancer impacts patients' functional status in terms of daily activities, physical ability, and ability to take care of themselves. The Eastern Cooperative Oncology Group (ECOG) Performance Status scale is a widely used method to assess PS among cancer patients. Table 1.3 displays the numbering scale for this measure. [5, 17] The cut-off used to determine recommended treatment for lung cancer according to the National Comprehensive Cancer Network (NCCN) guideline is 2 (0-2, 3-4). [5] An inter-observer variability study showed a highly consistent rating when oncologists used the ECOG PS measure with 2 as the cut-off to assess cancer patients' functional status. [17]

Table 1.3. ECOG Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry out any selfcare; totally confined to bed or chair
5	Dead

Source: Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5: 649-655.

1.4 Epidemiology of lung cancer

1.4.1 Incidence and mortality

Lung cancer is an enormous global health burden. About one in five cancer patients (~1.8 million) died of lung cancer globally in 2020, more than any other type of cancer. [18] [19] [20] [21] In 2020, an estimated 2.2 million people were newly diagnosed with lung cancer, accounting for 11.4% of the total new cancer cases that year. The incidence and mortality rates are geographically diverse. In general, incidence rates in 2020 were 3- to 4-fold higher in developed

countries versus developing countries. However, the pattern may shift to less developed countries in the future due to the success of smoking cessation programs in developed countries and tobacco epidemic evolution in low-income and middle-income countries. [22, 23] Incidence and mortality rates are roughly 2 times higher in men than in women. Among men, the highest incidence rates are observed in Micronesia/Polynesia, Eastern and Southern Europe, Eastern Asia, and Western Asia, with Turkey having the highest rate. Among women, the highest incidence rates are observed in North America, Northern and Western Europe, Micronesia/Polynesia, and Australia/New Zealand, with Hungary having the highest rate (Figure 1.1).

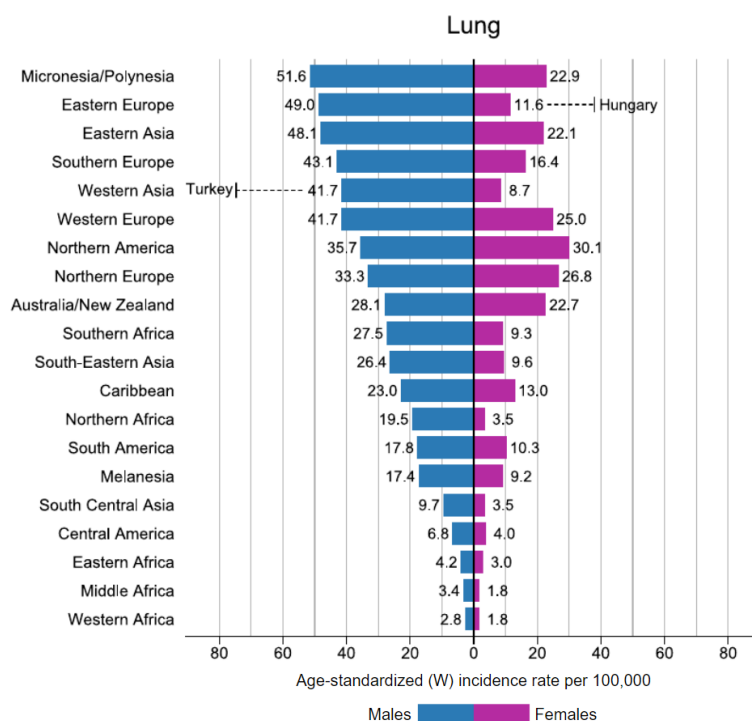


Figure 1.1 Region-specific age-standardized incidence rates by sex for lung cancer among men and women in 2020

Rates are shown in descending order of the world (W) age-standardized rate in men, and the highest national rates among men and women are superimposed. Data source: GLOBOCAN 2020

Source: Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, & Bray F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 71(3), 209-249.

Despite great efforts in lung cancer prevention, screening, and new innovations in diagnosis and treatment over the years, lung cancer was still the third most commonly diagnosed cancer (227,875) and the leading cause of cancer death (138,225) in 2020 in the United States. [19] Due to the aging population, lung cancer cases rise while the age-adjusted incidence rates decline over the years. The incidence rates of lung cancer steadily decreased from 59.8 per 100,000 in 2014 to 47.1 per 100,000 in 2020 (Table 1.4). [19] The death rates accordingly decreased from 42.2 per 100,000 in 2014 to 31.8 per 100,000 in 2020.

Table 1.4. Annual numbers and rates of incidence and death of lung cancer, United States, 2014-2020

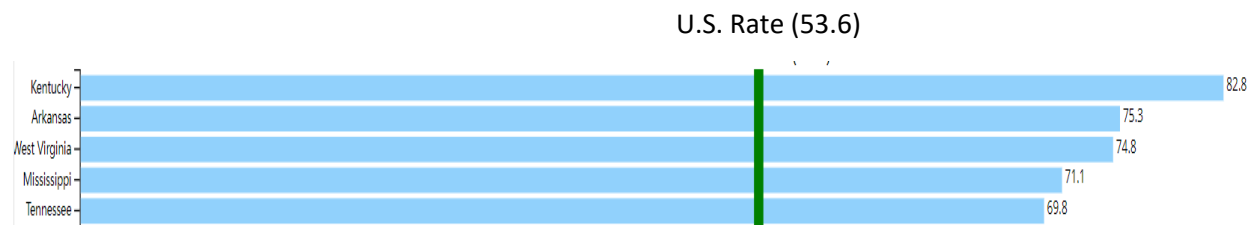
Year	2014	2015	2016	2017	2018	2019	2020
Incidence Number	221,328	224,924	225,271	227,669	226,789	228,844	227,875
Incidence Rate	59.8	59.2	57.9	56.9	55.2	54.3	47.1
Death Count	155,526	153,718	148,869	145,849	142,080	139,601	138,225
Death Rate	42.2	40.7	38.5	36.7	34.8	33.4	31.8

Note: * Rates are the number of cases (or deaths) per 100,000 people and are age-adjusted to the 2000 U.S. standard population (19 age groups – Census P25–1130).

Source: U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2022 submission data (1999-2020); U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; Accessed at: www.cdc.gov/cancer/dataviz, released in June 2023.

Geography is one factor related to the distribution of lung cancer cases and deaths. According to recent data from the Centers for Disease Control and Prevention (CDC) and United States cancer statistics, new lung cancer cases are concentrated in the Southeast. [19, 24] In 2018, the top five states for lung cancer incidence rate are Kentucky (82.8), Arkansas (75.3), West Virginia (74.8), Mississippi (71.1), and Tennessee (69.8) (Figure 1.2a). These states are also leading states for lung cancer deaths, except for Tennessee (Figure 1.2b). This pattern could be explained by local industry type, poverty, and poor health outcomes in the region. In Texas, there

were 13,530 new lung cancer patients reported (47/100,000) and 8,725 patients died of lung cancer in 2018, with both being below the average national rates.



Source: America Foundation of Lung, Lung Cancer Rates in the United States, 2021. Accessed at: <https://lcfamerica.org/research-grants/latest/research/lung-cancer-rates-in-the-united-states/>. October 2021.

Figure 1.2a Top 5 states for lung cancer incidence rate in the United States in 2018

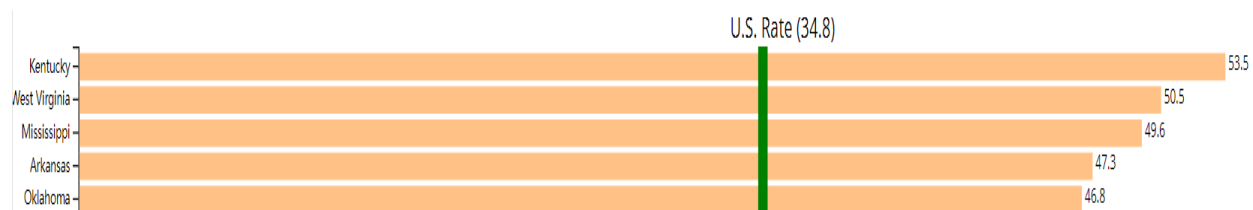


Figure 1.2b Top 5 states for lung cancer death rate in the United States in 2018

Source: America Foundation of Lung, Lung Cancer Rates in the United States, 2021. Accessed at: <https://lcfamerica.org/research-grants/latest/research/lung-cancer-rates-in-the-united-states/>. October 2021.

Gender, age, and race/ethnicity are also associated with differences in risk of lung cancer and death (Table 1.5). Lung cancer is more likely to occur among men than women. [19] Although more men than women died of lung cancer each year, the age-adjusted cancer death rate among men steadily decreased after 1990, while a progressively decreasing trend was observed after 2000 among women. [20] These trends are probably related to smoking prevalence which peaked about 2 decades earlier in men than in women. [25] With respect to race and ethnicity, white and black Americans are more likely to contract lung cancer than American Indian and Alaska natives,

Asians and Pacific Islanders, and Hispanics. [19, 20] Lung cancer is a disease of aging with a median diagnosis age of 71. [26] The incidence of lung cancer increases with age regardless of gender and race. The peak incidence rates were among patients aged 75 to 84 (Figure 1.3).

Table 1.5. Age-adjusted incidence and mortality rates for lung cancer by race, and gender, U.S. 2015-2019

Year of Diagnosis	Incidence Rate			Mortality Rate		
	Both Sexes	Males	Females	Both Sexes	Males	Females
All Races	53.1	60.1	47.9	38.5	44.5	30.7
White	54.9	60.5	50.8	39.3	44.7	32.0
Black	53.7	69.3	43.3	40.1	52.4	28.3
Asian/Pacific Islander	35.7	45.0	28.7	21.2	26.7	15.8
American Indian/Alaska Native	37.7	40.9	35.5	32.1	36.2	27.0
Hispanic	28.6	34.4	24.6	16.8	22.1	11.8
Non-Hispanic	-	63.6	51.2	-	46.8	32.6

Note: SEER 21 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey, Georgia excluding ATL/RG, Idaho, New York, and Massachusetts).

Rates are per 100,000 and age-adjusted to the 2000 US standard population (19 age groups - Census P25-1130).

Source: Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2018/, based on November 2020 SEER data submission, posted to the SEER web site, April 2021.

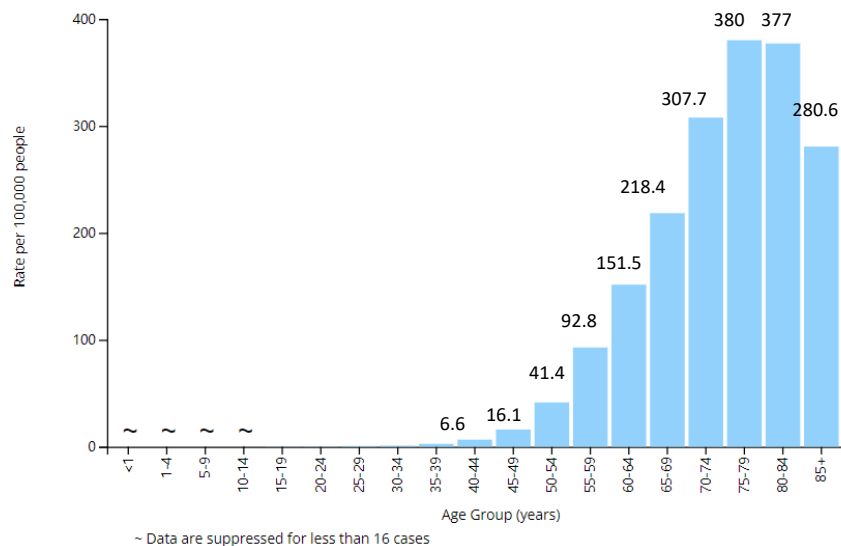


Figure 1.3. Rate of new cases of lung cancer by age group, U.S. 2018

Note: Rates are the number of cases per 100,000 people and are age-adjusted to the 2000 U.S. standard population (19 age groups – Census P25–1130).

Source: U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2022 submission data (1999-2020): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; Accessed at: www.cdc.gov/cancer/dataviz, released in June 2023.

1.4.2 Survival

Lung cancer patients have poor survival. The overall 5-year survival for lung cancer patients is only 22.9%. [20] The 5-year survival rate is nearly 60% when lung cancer is diagnosed at a localized stage (stage I-stage IIIA); however, only 18% of lung cancer patients are diagnosed with lung cancer at an early stage. As the disease progresses to stage IIIB (regional metastasis), the 5-year survival rate falls to half that of localized lung cancer patients. Among lung cancer patients with distant metastasis (stage IV), few patients are alive after 5 years regardless of gender (Both sexes: 6.7%, Males: 5.4%, Females: 8.1%) (Table 1.6).

Table 1.6. Five-year relative survival (percent) for lung cancer by stage at diagnosis, race, and sex, 2011-2017

Stage at Diagnosis	All Races			Whites			Blacks			Other Races		
	Both Sexes	Males	Females	Both Sexes	Males	Females	Both Sexes	Males	Females	Both Sexes	Males	Females
All Stages	22.9	19.2	26.9	22.8	19.2	26.8	20.7	17.2	24.9	28.6	24.6	33.3
Localized	56.6	50.6	61.8	59.7	50.6	64.5	55.6	47.4	59.7	66.9	60.2	73.1
Regional	31.3	27.8	35.2	32.4	27.5	36.1	32.4	27.0	34.5	40.3	34.9	47.0
Distant	6.7	5.4	8.1	5.9	5.1	7.3	6.5	5.6	8.3	13.1	11.3	15.2
Unstaged	13.7	12.2	15.3	8.8	11.5	9.8	10.4	11.5	14.2	20.8	20.1	21.4

Source: U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2020 submission data (1999-2018): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz, released in June 2021.

Lung cancer is known as a disease of aging. The 5-year survival for lung cancer patients decreases with increased age regardless of gender and race (Table 1.7) [20]. The age of 65 is a watershed age. For lung cancer, the 5-year survival for patients aged <65 is 26.6% which is higher than the overall survival rate for lung cancer, while the 5-year survival for patients aged 65+ is poorer (21.1%). In general, females had a superior survival outcome compared to males regardless of age and race. The 5-year survival was higher for females (26.9%) than for males (19.2%). White Americans have consistently better survival outcomes compared to Black Americans. These variations largely reflect differences in exposure to risk factors (e.g., smoking) and barriers to lung cancer prevention and early detection.

Table 1.7. Five-year relative survival (percent) for lung cancer by age at diagnosis, race, and sex, 2011-2017

Age at Diagnosis	All Races			Whites			Blacks		
	Both Sexes	Males	Females	Both Sexes	Males	Females	Both Sexes	Males	Females
All Ages	22.9	19.2	26.9	22.8	19.2	26.8	20.7	17.2	24.9
Ages <45	39.4	34.3	44.4	42.2	36.3	47.8	29.2	26.0	34.6
Ages 45-54	27.2	22.2	32.3	27.0	22.3	31.4	26.1	21.0	31.4
Ages 55-64	25.6	21.0	31.2	25.5	20.9	31.0	24.4	20.0	30.1
Ages 65-74	24.7	21.0	28.8	25.1	21.3	29.1	20.9	17.7	24.4
Ages 75+	17.2	14.5	19.6	17.4	14.7	19.8	14.3	10.9	16.8
Ages <65	26.6	21.9	32.2	26.5	21.8	31.9	25.1	20.5	30.6
Ages 65+	21.1	18.0	24.1	21.3	18.3	24.3	18.3	15.4	21.0

Source: U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2020 submission data (1999-2018); U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz, released in June 2021

1.5 Risk factors

The disparities in lung cancer incidence and mortality with respect to age, sex, race/ethnicity, and disease stage have been described in the previous section. These factors are prognostic factors for lung cancer occurrence. Other risk factors for lung cancer, including smoking, air pollution, family history, and comorbidity, will be discussed in this section.

1.5.1 Smoking

In 1964, the US Surgeon General concluded that “cigarette smoking is a cause of lung cancer in men, and a suspected cause of lung cancer in women.” [27] Since Richard Doll and Austin Hill first published a study stating that lung cancer was associated with smoking in 1950, substantial evidence further strengthened the notion that smoking was the predominant risk factor for lung cancer. [26, 27, 28, 29, 30, 31, 32, 33, 34] The relationship between smoking and lung cancer has been thoroughly investigated. Schuller et al. summarized preclinical and clinical data supporting the notion that smoking increased the risk for the development of small cell lung carcinoma, squamous cell carcinoma and pulmonary adenocarcinoma (PAC). The study demonstrated that the activation of nicotinic acetylcholine receptors and beta-adrenergic receptors by nicotine and nicotine-derived nitrosamines were the major driving forces of PAC development. The nicotine-derived nitrosamines may additionally cause mutations in the K-RAS and p53 genes and thus increased the chance of PAC development. [35]

A systematic meta-analysis demonstrated heterogeneous relative risk (RR) values among 287 studies with all showing a positive association between smoking and lung cancer (random-effects RR, 95% CI; ever smoking: 5.50, 5.07-5.96; current smoking: 8.43, 7.63-9.31; ex-smoking: 4.30, 3.93-4.71; and pipe/cigar only smoking: 2.92, 2.38-3.57). [36]

More studies have added solid evidence on the causal relationship between smoking and lung cancer. A longitudinal cohort study indicated that current smokers (RR, 95% CI: light: 7.06, 3.50-14.23; moderate: 13.06, 6.60-25.74; heavy: 26.55, 13.40-52.63) and lifetime persistent smokers (RR: 11.45, 95% CI: 4.39-29.87) had a higher risk of lung cancer mortality compared to non-smokers. [34] A longer duration of smoking (RR: 1.10, 95% CI: 1.03-1.17) and higher numbers of pack-years (RR: 1.02, 95% CI: 1.01-1.02) were associated with a higher risk of lung cancer mortality compared to non-smokers. Pesch and his colleagues also found that the relative risk of lung cancer was high among current smokers. Pesch et al. used the largest observational database of lung cancers in Europe and Canada (SYNERGY) including 13,169 cases and 16,010 controls between 1985 and 2005 and found that the odds of lung cancer for current smokers were about 23 times and 7 times greater than the odds for non-smokers in men and women, respectively. [37]

Smoking-related lung cancer risk increases with smoking intensity (cigarettes per day) and the cumulative exposure (pack-years) increases. Compared to never smokers, current smokers who smoked ≥ 20 cigarettes per day had a 3.3-fold increased risk of developing a second smoking-associated cancer among stage I lung cancer survivors (HR: 3.26, 95% CI: 0.92-11.6). In current smokers, age-adjusted odds ratios (OR) were higher for SqCC (Males: OR: 45.6, 95% CI: 34.3-60.6; Females: OR: 13.6, 95% CI: 10.5-17.7) compared to AdCa (Males: OR: 10.8, 95% CI: 8.7-13.3; Females: 4.2, 95% CI: 3.5-5.0). The relative risks of lung cancer were high among current smokers who smoked more than 30 cigarettes/day, smoked no less than 60 pack-years, and had more than 60 years smoking history. A pooled prospective study by Shiels et al. showed that 40% of stage I lung cancer survivors who developed a second cancer were current smokers. [32] The risk of developing a second smoking-associated cancer increased across pre-diagnostic smoking

status levels (never smoker, former smoker <20 cigarettes per day, former smoker $\geq$ 20 cigarettes per day, current smoker <20 cigarettes per day, current smokers $\geq$ 20 cigarettes per day) and pack-years smoked; however, this increasing trend was not statistically significant.

Gu et al. examined the association between time to first cigarette after waking (TTFC) and lung cancer. [33] They found that TTFC was an independent factor associated with lung cancer. The ORs of lung cancer for smokers with a TTFC of 60 or fewer minutes (31 to 60 minutes, 6 to 30 minutes, and 5 or fewer minutes) were 2.5 to 3.5 times higher than for smokers with a TTFC greater than 60 minutes. They also found that the incidence of lung cancer was consistently higher for smokers with a TTFC of 60 or fewer minutes compared to smokers with a TTFC greater than 60 minutes, regardless of smoking intensity (cigarettes per day).

Not only is smoking a crucial factor for lung cancer, the association between exposure to secondhand smoke and lung cancer was established. A study by Kim et al., the largest study to date on secondhand smoke, used pooled data from 18 case-control studies in the International Lung Cancer Consortium (ILCCO), and revealed that the risk of lung cancer for people who were ever exposed to secondhand smoke was 1.3 times that for never smokers. [29] The risks were similar for AdCa (OR: 1.41) and SqCC (OR: 1.48).

From another point of view, many studies have shown that patients with lung cancer benefited from smoking cessation with improved survival and decreased mortality. [38, 39, 40, 41] These studies indicated indirectly the causal relationship between smoking and lung cancer, and highlighted the importance of smoking cessation as well.

1.5.2 Environment

Besides smoking, air pollution was identified as an important risk factor for lung cancer as well. [42, 43] In Global Cancer Statistics 2020, the editors indicated that the high lung cancer mortality in Eastern Asian countries, such as China, was attributable to outdoor ambient particulate matter with a diameter of less than $2.5\mu\text{m}$ ($\text{PM}_{2.5}$). [21] Li and colleagues at the University of California and Zhongshan Hospital (China) reviewed epidemiological studies and found that PM-induced epigenetic changes may play important roles in the pathogenesis of lung cancer and mortality independent of smoking. [44]

Using data from 17 cohort studies in Europe collected by the European Study of Cohorts for Air Pollution Effects (ESCAPE), Raaschou-Nielsen and colleagues estimated the long-term effect (average follow-up: 12.8 years) of air pollution on the risk of lung cancer. [43] Their study showed a statistically significant relationship between the presence of particulate matter with a diameter of less than $10\mu\text{m}$ (PM_{10}) and the risk of lung cancer (hazard ratio (HR): 1.22, 95% CI: 1.03-1.45 per $10\mu\text{g}/\text{m}^3$ increase) and a borderline significant relationship between $\text{PM}_{2.5}$ and the risk of lung cancer (HR: 1.18, 95% CI: 0.96-1.46) while controlling for covariates. The association was stronger for risk of AdCa compared to SqCC (PM_{10} : HR: 1.51, 95% CI: 1.10-2.08; $\text{PM}_{2.5}$: HR: 1.55, 95% CI: 1.05-2.29).

A large-scale prospective study conducted by the American Cancer Society as part of the Cancer Prevention II study established the association between particulate air pollution and sulfur oxide-related air pollution and lung cancer mortality. [45] The study showed that the risk of lung cancer-related death increased 14% for each $10\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration (RR: 1.14, 95% CI: 1.04-1.23). In a follow-up study of the Cancer Prevention II study, Turner et al. further examined the association between $\text{PM}_{2.5}$ and lung cancer mortality among non-smokers.[49] With

a longer study time (26-year follow-up) and a larger cohort, the study revealed that the risk of lung cancer mortality among non-smokers increased 15 to 27% for each 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration (1979-1983: RR: 1.15, 95% CI: 0.99-1.35; 1999-2000: RR: 1.27, 95% CI: 1.03-1.56), which suggested that non-smokers are at risk from the harmful effects of particulate air pollution. The study also showed that the association between $\text{PM}_{2.5}$ and lung cancer mortality was no different between male and female non-smokers.

In summary, air pollution is associated with a higher risk of lung cancer incidence and mortality, especially for non-smokers and AdCa.

1.5.3 Family history

Although smoking and air pollution are the two predominant risk factors for lung cancer, familial factors cannot be ignored. Many clinical-based, population-based, and registry-based studies have established that family history of cancer, especially in first-degree relatives, increases the risk of developing lung cancer and death, decreases the response rate to chemotherapy, and worsens disease prognosis. [46, 47][51-61] In a pooled analysis from the International Lung Cancer Consortium which included 24 case-controlled studies (24,380 lung cancer cases and 23,305 healthy controls), researchers highlighted the importance of family history of lung cancer in the development of lung cancer after controlling for smoking and other confounders. A positive family history of lung cancer (first-degree relative) was associated with a 1.51-fold increase in risk of lung cancer (OR: 1.51, 95% CI:1.39-1.63). The association was greater for smokers (OR: 3.19, 95% CI: 2.03-5.00) and those with a sibling with lung cancer history (OR: 1.82, 95% CI: 1.62-2.05). [47]

Family history of cancer may affect clinical features and treatment outcomes as well. [48, 49] Using a hospitalized population in China, Li et al. found that most NSCLC patients whose first-degree and second-degree relatives had a history of lung cancer were female nonsmokers, diagnosed with NSCLC at an early age, and at an advanced disease stage (stage IIIB and stage IV). [49] They also found that patients' complete response and partial response to first-line chemotherapy was lower if their first-degree or second-degree relatives had a history of lung cancer compared to those with no family history of lung cancer. They found that patients with a family history of lung cancer experienced a better overall survival (OS) at an early disease stage but not at an advanced disease stage. Isla et al. also found a longer median overall survival time among Spanish women with lung cancer and with a family history of lung cancer. [48] These results could be explained by a higher awareness among these patients with a positive family history of lung cancer suggesting that they are more likely to undertake screening and receive treatment early.

Previous studies also found that familial inheritance is a stronger contributing factor for lung cancer for non-smokers and females. [50, 48] Familial cancer could be caused by genetic and environmental factors. [51] Many studies have established an association between family history of cancer and mutation in epidermal growth factor receptors (EGFR) in NSCLC. [52] [53] [50] NSCLC patients with a family history of lung cancer might have a significantly higher incidence of EGFR mutation. In addition to genetic factors, family members might share the same living habits and living environment, which also can lead to a higher risk of lung cancer. [54]

1.5.4 Comorbidity

Lung cancer is a disease of aging. Elderly patients typically have more comorbidities. Prior studies have shown that comorbidity has a negative impact on lung cancer survival and prognosis. [55, 56] Comorbidities identified as important factors related to lung cancer survival are HIV/AIDS, tuberculosis, previous metastatic cancer, thyroid/glandular diseases, electrolyte imbalance, anemia, other blood diseases, dementia, neurologic disease, congestive heart failure, chronic obstructive pulmonary disease (COPD), asthma, pulmonary fibrosis, liver disease, gastrointestinal bleeding, renal disease, connective tissue disease, osteoporosis, and peripheral vascular disease. [56] Among these diseases, COPD is the most common lung cancer comorbidity. In a study by Shah et al., the authors investigated the impact of COPD on overall survival among Medicare enrollees diagnosed with NSCLC between 2006 and 2010. [57] They found that the median OS was significantly shorter in the COPD group compared with non-COPD group regardless of stage of NSCLC (Stage I: 692 days vs 1,130 days, $P < 0.0001$; Stage II: 473 days vs 627 days, $P < 0.0001$; Stage III: 224 days vs 229 days; $P < 0.0001$; Stage IV: 106 days vs 112 days, $P < 0.0001$). COPD patients exhibited an 11% higher risk of death than non-COPD patients.

Using number of comorbid conditions, the Charlson Comorbidity Index (CCI), the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), and the Simplified Comorbidity Score System (SCSS) are common ways to measure the impact of comorbidities on lung cancer treatment choice, treatment outcome, and prognosis. [55, 56]

Firat et al. found that the CIRS-G (severity index) and the CCI were independently associated with OS among stage III NSCLC patients.[67] However, the association was mediated by other pathophysiologic factors. Another pooled study of two prospectively randomized trials of systemic chemotherapy conducted by the National Cancer Institute of Canada Clinical Trials

Group (NCIC CTG) also found that comorbidity measured by the CCI was independently associated with OS and disease-specific survival (DSS).[68] However, the study samples in these clinical trials were selected so that a small number of patients had a CCI score greater than 1. Thus, the impact of CCI on OS may be underestimated.

1.6 Lung cancer treatment

In this section, general treatment options will be summarized according to NCCN Non-Small Cell Lung Cancer Practice Guidelines and Small Cell Lung Cancer Practice Guidelines. A discussion of chemotherapies, targeted therapies, and immunotherapies will be provided next.

1.6.1 Stage I, stage II and stage IIIA

The initial treatment for patients in stage I, stage II, and stage IIIA is surgical exploration and resection plus mediastinal lymph node dissection or systematic lymph node sampling if pretreatment evaluation indicates that patients are medically operable. [8] Depending on findings at surgery, adjuvant treatment will be provided. Adjuvant treatment for stage IA patients is either watchful waiting (if margins are negative), or re-resection or radiation therapy (if margins are positive). For stage IB and stage IIA patients, adjuvant treatment includes watchful waiting or chemotherapy for high-risk patients (if margins are negative), or re-resection with/without chemotherapy, or radiation therapy with/without chemotherapy (if margins are positive). For patients in stage IIB, stage IIIA, and stage IIIB, chemotherapy is recommended if pretreatment evaluation shows margins are negative. Re-resection with chemotherapy, or chemoradiation, or concurrent chemoradiation are recommended depending on existence of residual tumors for patients with positive margins (Figure 1.4 and Figure 1.5).

For patients who are medically inoperable, definitive radiation therapy including stereotactic ablative radiotherapy (SABR) is recommended for stage IA patients. [8] For patients in stage IB, stage II (A and B), and stage IIIA, definitive radiation therapy including SABR is preferred for patients without regional lymph node metastases; definitive chemoradiation is preferred for patients with metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension. If pretreatment evaluation indicates a positive result on mediastinal nodes, the initial treatment includes chemotherapy, sequential chemotherapy with radiation therapy, sequential chemoradiation, and concurrent chemoradiation.

Stage	TNM score	Surgery	Radiation therapy	Chemoradiation
1A	T1, N0, M0	•	•	
1B	T2a, N0, M0	•	•	
2A	T2b, N0, M0	•	•	
2B	T3, N0, M0 (no invasion)	•	•	
2B	T3, N0, M0 (invasion)			
	T1, N1, M0	•		•
	T2, N1, M0			
3A	T3, N1, M0			
	T4, N0, M0			
	T4, N1, M0	•		•
	T1, N2, M0			
3B	T2, N2, M0			
	T3, N2, M0 (no invasion)	•		•
3B	T3, N2, M0 (invasion)			
	T4, N2, M0			
	T1, N3, M0			•
	T2, N3, M0			
3C	T3, N3, M0			•
	T4, N3, M0			

Figure 1.4 Initial treatment options for lung cancer by stage

Source: National Comprehensive Cancer Network; NCCL guidelines for patients: Non-small cell lung cancer early and locally advanced; 2021. National Comprehensive Cancer Network 2021. Accessed at www.nccn.org, November 2021

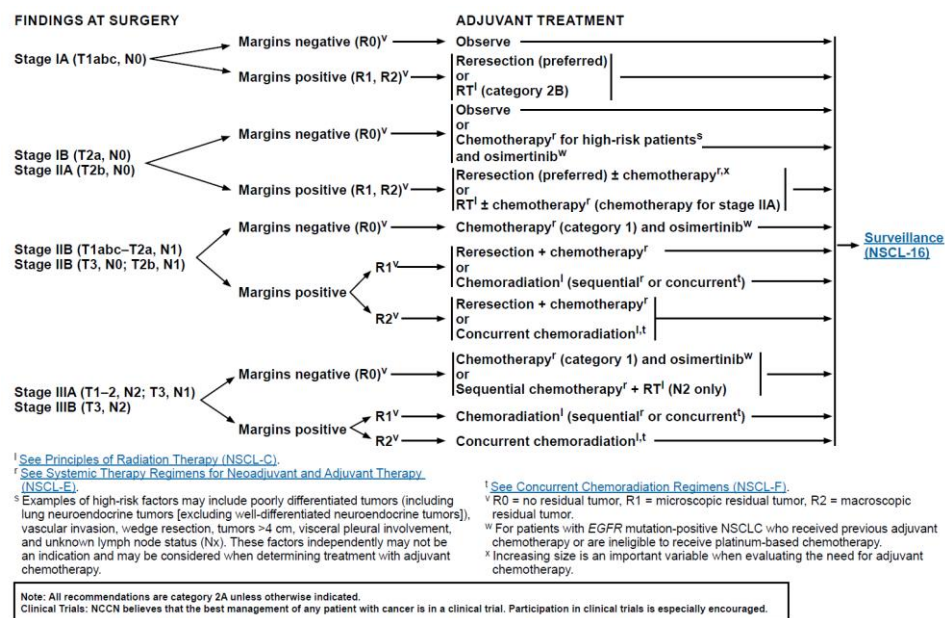


Figure 1.5 Adjuvant treatment for NSCLC stage I, stage II, and stage IIIA

RT: radiation therapy

Source: National Comprehensive Cancer Network; NCCN clinical guideline in oncology: Non-small cell lung cancer version 6.2021. National Comprehensive Cancer Network 2021. Accessed at www.nccn.org, November 2021

1.6.2 Stage IIIB and stage IV

For patients in stage IIIB (T1-2, N3) and stage IIIC (T3, N3), the initial treatment is based on the status of N3 and metastasis. [8] The treatment for patients with N3 negative is the same as the treatment for stage I to stage IIIA as discussed above. For patients with N3 positive, definitive concurrent chemoradiation and durvalumab are recommended as initial treatment and subsequent treatment. Stage IIIB (T4, N2) and stage IIIC (T4, N3) patients with negative results on the contralateral mediastinal node and further confirmed negative results on the ipsilateral mediastinal node should receive chemotherapy and osimertinib or sequential chemotherapy with radiation therapy or chemoradiation or concurrent chemoradiation. If the test for the contralateral mediastinal node or the ipsilateral mediastinal node is positive, definitive concurrent chemotherapy is recommended. For patients at stage IIIB and stage IIIC with metastatic disease, the treatment recommendation is based on metastatic sites (Figure 1.5, Figure 1.6, and Figure 1.7).

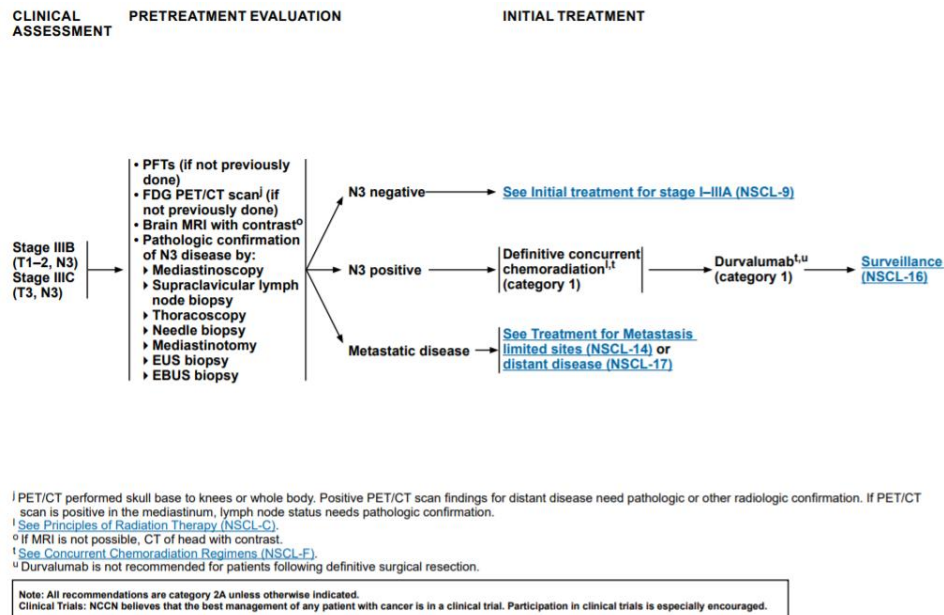


Figure 1.6 Pretreatment evaluation and initial treatment for NSCLC stage IIIB (T1-2, N3) and stage IIIC (T3, N3)

PFTs: pulmonary function tests, FDG PET/CT: fluorodeoxyglucose-positron emission tomography/ Computed Tomography, EUS: endoscopic ultrasound, EBUS: endobronchial ultrasound.

Source: National Comprehensive Cancer Network; NCCN clinical guideline in oncology: Non-small cell lung cancer vision 6.2021. National Comprehensive Cancer Network 2021. Accessed at www.nccn.org, November 2021

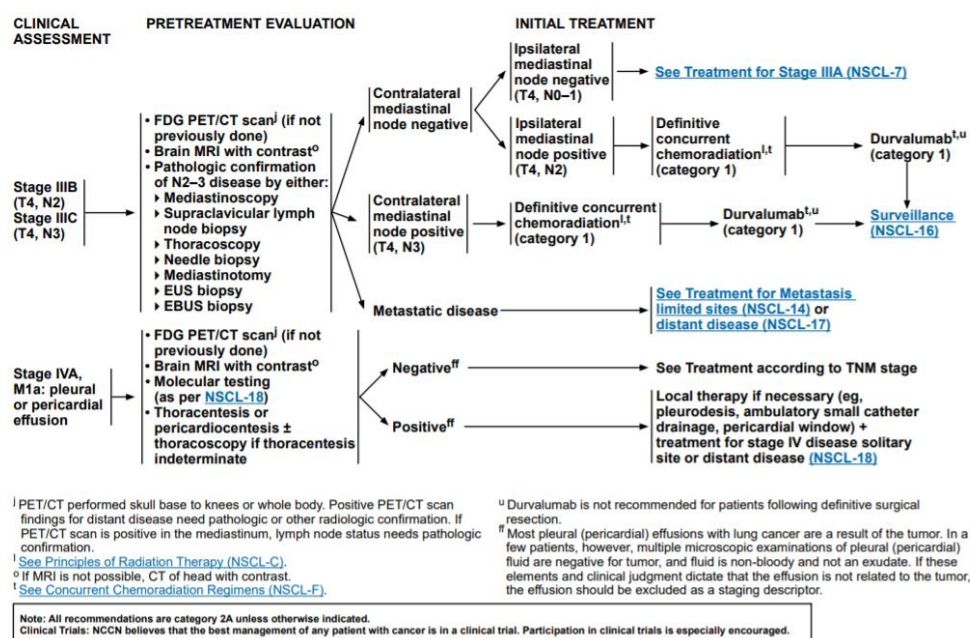


Figure 1.7 Pretreatment evaluation and initial treatment for NSCLC stage IIIB (T4, N2-3) and stage IVA, M1a

FDG PET/CT: fluorodeoxyglucose-positron emission tomography/Computed Tomography, EUS: endoscopic ultrasound, EBUS: endobronchial ultrasound.

Source: National Comprehensive Cancer Network; NCCN clinical guideline in oncology: Non-small cell lung cancer version 6.2021. National Comprehensive Cancer Network 2021. Accessed at www.nccn.org, November 2021

Treatment for NSCLC stage IV depends on the status of metastasis, molecular pathology, and patients' PS. [8] Figures 1.7 and 1.8 illustrate the treatment pathway for stage IV NSCLC. Patients in stage IV (M1a) may receive surgical resection plus mediastinal lymph node dissection or systematic lymph node sampling, or definitive concurrent chemotherapy with or without radiation if pretreatment evaluation showed negative results. Otherwise, patients will receive local therapy or patients will be tested for genetic mutation and be treated accordingly. For patients in stage IV (M1b) and with a good PS (0-2), treatment is determined based on metastasis site. Stereotactic radiosurgery or surgical resection is recommended for patients with brain metastases. Treatment of thoracic disease is recommended for patients with metastases to other sites. If patients

had multiple metastases, they will be treated according to molecular test results. For patients in stage IV (M1b) and with a poor PS (3-4), systemic treatment is recommended.

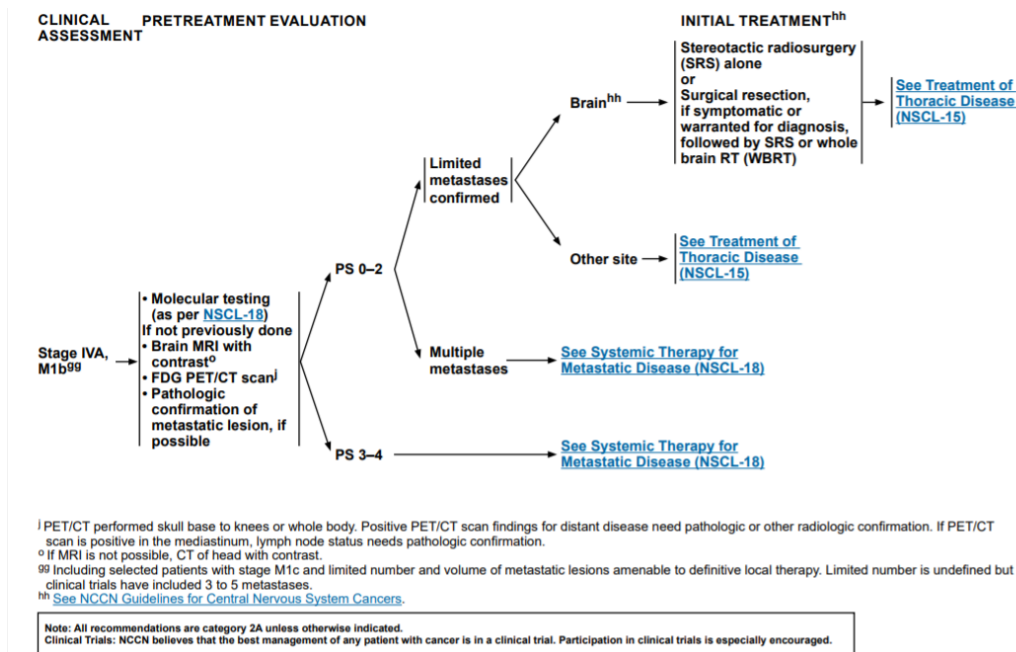


Figure 1.8 Pretreatment evaluation and initial treatment for NSCLC stage IV, M1b

FDG PET/CT: fluorodeoxyglucose-positron emission tomography/Computed Tomography

Source: National Comprehensive Cancer Network; NCCN clinical guideline in oncology: Non-small cell lung cancer vision 6.2021. National Comprehensive Cancer Network 2021. Accessed at www.nccn.org, November 2021

Regarding specific medication options, systemic therapy includes platinum agents (e.g., cisplatin, carboplatin), taxanes (paclitaxel, albumin-bound paclitaxel, and docetaxel), vinorelbine, etoposide, pemetrexed and gemcitabine. [8] Systemic therapy most often uses a combination of 2 chemotherapy drugs, such as cisplatin- or carboplatin-based chemotherapies. If patients maintain a good response to initial chemotherapy or their disease condition is stable, 4-6 cycles of chemotherapy followed by continuation maintenance or switch maintenance therapy are recommended. Recommended continuation maintenance therapy includes bevacizumab,

pemetrexed, bevacizumab with pemetrexed, or gemcitabine. Recommended switch maintenance therapy includes pemetrexed and observation. Otherwise, subsequent therapy will be initiated if disease progresses to late stage.

According to the recent NCCN clinical guideline, treatment for patients with advanced/metastatic NSCLC should be based on molecular and biomarker test results. [8] For patients who have confirmed gene mutation, targeted therapy is preferred to chemotherapy. Patients who have epidermal growth factor receptor (EGFR) mutations, most commonly in exon 19 and exon 20, are referred to as having sensitizing EGFR. Small molecular tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, and afatinib, dacomitinib, osimertinib, erlotinib plus ramucirumab and erlotinib plus bevacizumab are recommended agents for first-line treatment of patients with NSCLC who have sensitizing EGFR mutations. Erlotinib is the most frequently used TKI. Because patients usually become resistant to erlotinib, gefitinib, and afatinib after 8-16 months, osimertinib is recommended as subsequent treatment for patients with exon 19 deletion and amivantamab-vmjw and mobovertinib for patients with exon 20 insertion mutation. Anaplastic lymphoma kinase (ALK) gene rearrangement and EGFR mutation are mutually exclusive. ALK gene rearrangement can be found in 2%-7% of patients with NSCLC in the US. Alectinib, brigatinib, ceritinib, crizotinib, and lorlatinib are recommended for patients with NSCLC who have ALK gene mutation, and alectinib, brigatinib, ceritinib, and lorlatinib are recommended as subsequent treatment. [8] KRAS mutation is the most common mutation in NSCLC; however, targeted therapy is not currently approved as first-line therapy for patients with KRAS mutations. Sotorasib is recommended for subsequent therapy. For ROS1 rearrangement positive patients, first-line therapies include ceritinib, crizotinib, and entrectinib. Subsequent therapies are lorlatinib and entrectinib.

Currently, the subsequent treatments for NSCLC have gradually moved from the era of chemotherapy/targeted therapy to the era of immunotherapy. [8] For patients with PD-L1 $\geq 1\%$, first-line therapies include pembrolizumab, (carboplatin or cisplatin)/pemetrexed/pembrolizumab (nonsquamous), carboplatin/paclitaxel/bevacizumab/atezolizumab (nonsquamous), carboplatin/(paclitaxel or albumin-bound paclitaxel)/pembrolizumab (squamous), carboplatin/albumin-bound paclitaxel/atezolizumab (nonsquamous), nivolumab/ipilimumab, nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin) (nonsquamous), and nivolumab/ipilimumab/pemetrexed/carboplatin (squamous). In addition to above treatments, atezolizumab and cemiplimab-rwlc are recommended as first-line therapy for patients with PD-L1 $\geq 50\%$.

1.6.3 SCLC

Treatment for SCLC depends on the status of metastasis and patients' PS. (Figure 1.9 and Figure 1.10) For all patients with SCLC, systemic therapy is an essential component of appropriate treatment. For patients with limited stage IIB to IIIC with good PS (0-2), recommended treatment consists of chemotherapy with concurrent thoracic radiotherapy. Etoposide plus cisplatin (EP) is the most commonly used initial chemotherapy for patients with limited stage SCLC. For patients with extensive stage SCLC, systemic therapy is the recommended treatment. Carboplatin plus etoposide is preferred for standard treatment for patients with extensive stage SCLC.

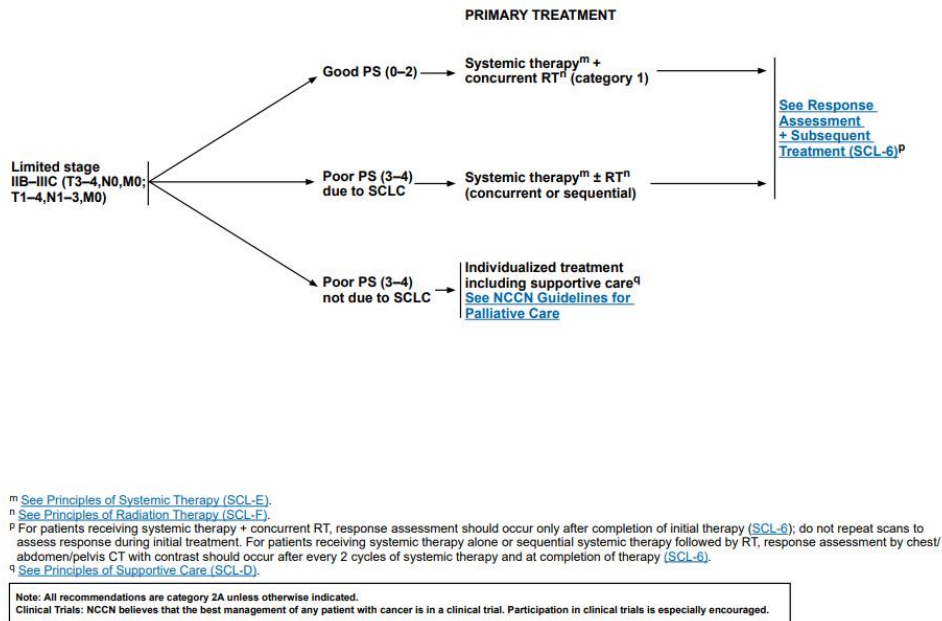


Figure 1.9 Primary treatment for limited stage SCLC

Source: National Comprehensive Cancer Network; NCCL clinical guideline in oncology: Small cell lung cancer vision 6.2021. National Comprehensive Cancer Network 2021. Accessed at www.nccn.org, November 2021

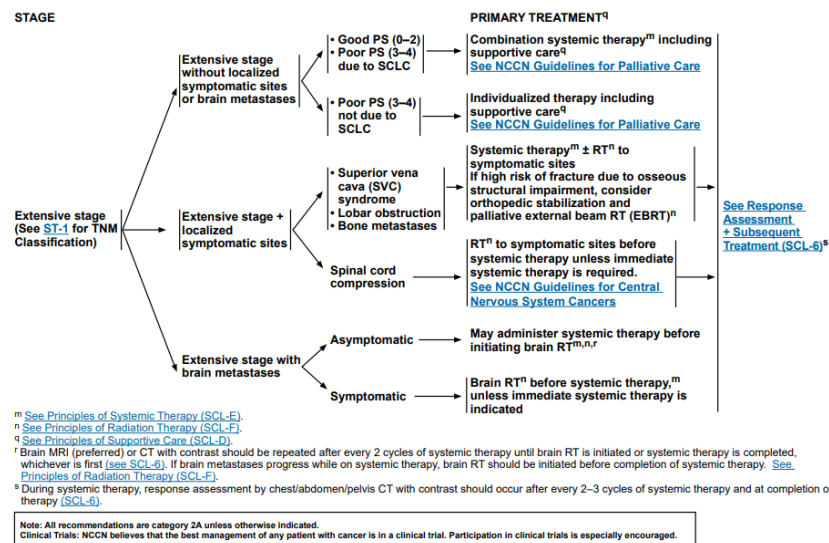


Figure 1.10 Primary treatment for extensive stage SCLC

Source: National Comprehensive Cancer Network; NCCL clinical guideline in oncology: Small cell lung cancer vision 6.2021. National Comprehensive Cancer Network 2021. Accessed at www.nccn.org, November 2021

1.7 Chemotherapy, targeted therapy, and immunotherapy for advanced NSCLC

1.7.1 The role of chemotherapy in clinical practice

Chemotherapy is the mainstay of treatment for lung cancer patients as neoadjuvant therapy, adjuvant therapy, and initial systematic treatment. Currently, platinum-based chemotherapies (cisplatin-based and carboplatin-based) are considered to be the standard first-line treatment for advanced NSCLC according to the National Comprehensive Cancer Network (NCCN). [8] The controversy about whether cisplatin-based and carboplatin-based treatments are equally effective for advanced NSCLC still exists. A number of clinical trials were conducted to assess the efficacy and safety of carboplatin-based chemotherapy compared to cisplatin-based chemotherapy for advanced NSCLC, but the study results were inconsistent. [58, 59, 60, 61, 62, 63] Additionally, these studies included different chemotherapy combinations and thus failed to conclude that carboplatin-based treatment could replace cisplatin-based treatment. Two meta-analyses were performed to assess results of combined studies and are summarized below. [64, 65]

A meta-analysis by Hotta et al. reported that cisplatin-based treatment had a better objective response rate (ORR)¹ compared to carboplatin-based treatment (OR: 1.36, 95% CI: 1.15-1.61, $p < 0.001$). [64] In contrast, cisplatin-based treatment only improved OS by 5% and it was not significantly different compared to carboplatin-based treatment (HR: 1.050, 95% CI: 0.907-1.216, $p = 0.515$). However, cisplatin and carboplatin had greatly different toxicity profiles. Cisplatin was more likely to cause severe nausea and vomiting (OR: 2.51, 95% CI: 1.76-3.56) while carboplatin was more likely to cause thrombocytopenia (OR: 0.58, 95% CI: 0.39-0.87). Both

¹ Objective response rate (ORR) is defined as proportion of patients with reduction in tumor burden of a predefined amount, according to U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER)

cisplatin and carboplatin led to neutropenia and nephrotoxicity. An updated meta-analysis conducted by Ardizzoni et al. in 2007 revealed comparable results. [65] Cisplatin-based treatment was associated with a higher ORR compared to carboplatin-based treatment (OR: 1.37, 95% CI: 1.16-1.61, $P < 0.001$). Neither treatment outperformed with respect to OS (HR: 1.07, 95% CI=0.99-1.15, $P = 0.100$). Regarding toxicity profile results, severe nausea and vomiting and nephrotoxicity occurred more frequently during cisplatin-based treatment, while thrombocytopenia was more common during carboplatin-based treatment. The two meta-analysis results indicated that the toxicity profile may play an important role when selecting appropriate treatment for patients with advanced NSCLC.

A meta-analysis by Castria et al. found no significant differences in OS and 1-year survival between cisplatin-based and carboplatin-based treatment among patients treated with third-generation treatments (paclitaxel, irinotecan, docetaxel, gemcitabine, and vinorelbine). [66] The toxicity profile results were similar to those reported by Hotta et al. and Ardizzoni et al. [64, 65] Using intent-to-treat analysis, Jiang et al. found that carboplatin-based treatment had a slightly lower ORR (RR: 0.91, 95% CI: 0.84-0.99, $P = 0.02$) but the survival outcome was not significantly different (RR:1.00, 95% CI: 0.94-1.07, $P = 0.93$) compared to cisplatin-based treatment. [67] Subgroup analysis comparing doublet treatment and triplet treatment separately showed no significant difference in terms of ORR and 1-year survival.

The management of advanced NSCLC has been changed as many studies showed maintenance therapy played a role after completion of first-line treatment. [68, 69] A meta-analysis by Zhang et al. concluded that chemotherapy given as maintenance therapy for advanced NSCLC could improve progression free survival (PFS) (OR: 0.43, 95% CI: 0.33-0.55, $P < 0.00001$) but not OS (OR:0.8, 95% CI: 0.59-1.07, $P = 0.13$). [70] After pemetrexed was approved as maintenance

therapy for nonsquamous NSCLC, several studies have shown the benefit of both switch maintenance and continuation maintenance strategies involving pemetrexed. [71, 72] The PARAMOUNT trial investigated treatment outcomes among patients who had not progressed after four cycles of first-line platinum chemotherapy (pemetrexed plus cisplatin) and continued maintenance therapy with pemetrexed or best supportive care. PFS was significantly improved in the arm receiving pemetrexed (median PFS: 4.1 months vs 2.8 months; HR: 0.62; 95% CI: 0.49-0.79; $P<.0001$). [72] Although grade 3-4 adverse events (anemia, neutropenia, and fatigue) were more common in the pemetrexed arm, the treatment was overall reasonably well tolerated. Another study showed that a switch maintenance strategy with pemetrexed could also have benefit. [71] Patients who had not progressed on four cycles of platinum with a taxane or gemcitabine were randomly assigned to receive pemetrexed plus best supportive care or placebo plus best supportive care. PFS and OS in the pemetrexed arm were significantly improved (median PFS: 4.3 months vs 2.6 months; $P<.0001$; median OS: 13.4 months vs 10.6 months; $P=.012$). Similar to the results from the PARAMOUNT trial, the frequency of grade 3-4 adverse events (neutropenia and fatigue) was higher in the pemetrexed arm; however, there were no treatment-related deaths reported and the treatment was considered well tolerated.

Most patients ultimately progress after completing first-line treatment and require further treatment. The options for subsequent treatment are limited. Docetaxel is the first approved second-line treatment for NSCLC. Studies have shown that single-agent therapy with docetaxel was associated with a survival benefit with fewer treatment-related adverse events. [73, 74]

1.7.2 The role of targeted therapy in clinical practice

Individualized therapy targeting molecular markers in the tumor provides new hope of improving treatment outcomes in the management of NSCLC since current platinum-based regimens have reached their “efficacy plateau.” [75, 76]

EGFR is the most studied target in lung cancer. EGFR TKIs, such as afatinib, erlotinib, and gefitinib, have been introduced into the first-line treatment for patients with advanced EGFR-mutated NSCLC. Clinical trials evaluating erlotinib or gefitinib in combination with either cisplatin or carboplatin have been conducted and have yielded favorable results for these agents. [77, 78] Afatinib has been shown to be efficacious in patients with advanced lung adenocarcinoma and EGFR mutations. [78] A phase III clinical trial reported that afatinib was associated with prolonged progression-free survival (PFS) compared to cisplatin plus pemetrexed (11.1 months vs. 6.9 months; HR: 0.58; 95% CI: 0.43-0.78; $p=.001$).

Regarding erlotinib, patients in the TRIBUTE study receiving carboplatin and paclitaxel with erlotinib and harboring EGFR mutation were observed to have an improved ORR compared to those with wild type tumors (53% vs. 18%, $p<0.001$). [79] Patients receiving erlotinib in addition to carboplatin and paclitaxel experienced a longer median time to progression (12.5 months vs. 6.6 months; 95% CI: 0.2-1.2; $p=0.092$) compared to patients receiving carboplatin plus paclitaxel in mutation-positive patients. Although the study was not able to identify a significant difference in survival because median survival was not reached among mutation-positive patients, it suggested that adding erlotinib to carboplatin and paclitaxel showed better clinical outcomes (ORR and time to progression) among patients with NSCLC and harboring EGFR. The TALENT phase III trial echoed the study results of the TRIBUTE study and showed increased OS and PFS in never-smokers receiving erlotinib. [80] A phase III trial (OPTIMAL) first confirmed the role of

erlotinib in advanced NSCLC patients with EGFR mutation. This clinical trial found that patients receiving erlotinib achieved prolonged PFS (13.1 months vs. 4.6 months) and a higher response rate (83% vs. 36%) compared to patients receiving chemotherapy. [81]

Regarding gefitinib, the Iressa Pan-Asia Study (IPASS) compared the efficacy of gefitinib and carboplatin plus paclitaxel in terms of OS and PFS. [82, 83] The study revealed that PFS was significantly longer among mutation-positive patients receiving gefitinib than those receiving carboplatin–paclitaxel (HR: 0.48; 95% CI: 0.34-0.67; $p < 0.001$), and significantly shorter among mutation-negative patients receiving gefitinib than among those receiving carboplatin–paclitaxel (HR: 3.85; 95% CI: 2.09-7.09; $P < 0.001$). However, no significant difference in OS between subgroups was found. The study indicated that gefitinib is a reasonable therapy option for patients with advanced NSCLC and EGFR mutation. However, platinum-based therapy is still the first option if EGFR is unknown.

Angiogenesis is known to be essential for the development and progression of cancer. VEGF is a critical mediator in tumor angiogenesis for NSCLC. Inhibition of tumor-related angiogenesis has become an attractive target for anticancer therapy. Bevacizumab, an inhibitor of VEGF, was approved for advanced non-squamous NSCLC based on phase II and III clinical trials (ECOG 4599). [84] The median survival was 12.3 months in patients receiving bevacizumab in addition to paclitaxel and carboplatin compared with 10.3 months in patients receiving paclitaxel and carboplatin only (HR: 0.79; 95% CI: 0.67-0.92; $P = 0.003$). The median PFS in the chemotherapy plus bevacizumab and chemotherapy alone groups was 6.2 and 4.5 months (HR: 0.66; 95% CI: 0.57-0.77; $P < 0.001$), with corresponding response rates of 35% and 15% ($P < 0.001$), respectively. A meta-analysis including ECOG4599 and three other clinical trials compared bevacizumab in addition to different platinum-doublets to platinum-doublets as first-line treatment

for advanced NSCLC. [85] This meta-analysis demonstrated that adding bevacizumab to platinum-doublets significantly improved OS (HR: 0.90; 95% CI: 0.81-0.99; P=0.03) and PFS (HR: 0.72; 95%CI: 0.66-0.79; P<0.001); however, the addition is also associated with an increased risk of grade $\geq$ proteinuria, hypertension, haemorrhagic events, neutropenia, and febrile neutropenia.

Clinical trials have shown superior survival and ORR results for ALK TKIs compared to chemotherapy. A phase III clinical trial (NCT01154140) found that crizotinib improved PFS (disease progression or death) by 55% compared to pemetrexed with either cisplatin or carboplatin in patients with advanced ALK-positive non-squamous NSCLC who had received no previous systemic treatment (median PFS: 10.9 months vs. 7.0 months; HR: 0.45; 95% CI: 0.35 to 0.60; P<0.001). [86] ORR was also improved in the crizotinib group (74% to 45%, P<0.001). In terms of safety and adverse events, crizotinib was associated with at least a 5% lower chance of fatigue, anemia, and neutropenia, but a 5% higher chance of vision disorder, diarrhea, and edema. Overall, the adverse events were manageable in the crizotinib group. Using the lung cancer module (QLQ-LC13) of the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (QLQ-C30), significant improvement in patient-reported outcomes were observed in the global quality of life, physical, social, emotional, and role functioning domains among patients receiving crizotinib. They also reported a delay in the worsening of lung-cancer symptoms and improved general health status scores using the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D).

Ceritinib was shown highly active among patients who progress on prior systemic therapy. According to a clinical trial (ASCEND-4), the risk of disease progression or death was reduced 45% among patients treated with ceritinib. [87] The overall response rate was 72.5% (95% CI:

65.5-78.7%) among those who received ceritinib and 26.7% (95% CI: 20.5-33.7%) among those who received chemotherapy.

1.7.3 The role of immunotherapy in clinical practice

The advancement of immunotherapy has heralded a new era of personalized NSCLC management. Nivolumab and pembrolizumab are the first two programmed cell death 1 (PD-1) agents approved by the FDA; these agents have been approved for first- and second-line treatment for patients with advanced NSCLC. [8]

The efficacy and safety of nivolumab in metastatic NSCLC was evaluated in CHECKMATE-017, a randomized open-label, multicenter trial in patients with metastatic squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen and in CHECKMATE-057, a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen. [88, 89] The study showed that the nivolumab group presented a longer median survival (9.2 m (7.3-13.3) vs. 6.0 m (5.1-7.3), HR=0.59 (0.43-0.81), p=0.0002 in CHECKMATE-017; 12.2 m (9.7-15.0) vs. 9.4 m (8.1-10.7), HR=0.73 (0.59-0.89), p=0.0015 in CHECKMATE-057) and PFS (3.5 m (2.1-4.9) vs. 2.8 m (2.1-3.5), HR=0.62 (0.47-0.81), p<0.004 in CHECKMATE-017; 2.3 m (2.2-3.3) vs. 4.2 m (3.5-4.9), HR=0.92 (0.77-1.11), p=0.39 in CHECKMATE-057) compared to the docetaxel group. More patients achieved better overall response in the nivolumab group compared to the docetaxel group (20% (14%-28%) vs. 9% (5%-15%), OR=2.64 (1.27-5.49), p=0.008 in CHECKMATE-017; 19% (15%-24%) vs. 12% (9%-17%), OR=1.68 (1.07-2.64), p=0.0246 in CHECKMATE-057). Treatment-related adverse events occurred less frequently in the nivolumab group. In the nivolumab group, no more than 10% of

patients had grade 3 or 4 treatment-related adverse events (TRAE) (7% in CHECKMATE-017 and 10% in CHECKMATE-057), while in the docetaxel group, over half of patients had grade 3 or 4 TRAE (55% in CHECKMATE-017 and 54% in CHECKMATE-057).

A randomized, open-label, phase 2/3 study (KEYNOTE-010) assessed the efficacy of docetaxel (75 mg/m² every 3 weeks) and pembrolizumab (2 mg/kg and 10 mg/kg every 3 weeks). [90] The clinical trial showed that the median survival time with pembrolizumab was significantly longer compared to docetaxel (median survival: 10.4 months with pembrolizumab 2 mg/kg, 12.7 months with pembrolizumab 10 mg/kg, and 8.5 months with docetaxel; pembrolizumab 2 mg/kg vs. docetaxel: HR: 0.88, 95% CI: 0.74-1.05; p=0.07; pembrolizumab 10 mg/kg: HR: 0.79, 95% CI 0.66-0.94; p=0.004). PFS was comparable between the pembrolizumab and docetaxel groups (3.9 months with pembrolizumab 2 mg/kg, 4.0 months with pembrolizumab 10 mg/kg, and 4.0 months with docetaxel).

Atezolizumab is a new treatment option for patients with PD-L1-positive, advanced NSCLC. In a randomized open-label, global multicenter trial in patients with metastatic NSCLC and progression on or after one prior platinum doublet-based chemotherapy (OAK), patients treated with atezolizumab showed superior survival outcome and ORR to the docetaxel group (OS:13.8m (11.8-15.7) vs. 9.6 m (8.6-11.2), HR=0.73 (0.62-0.87), P=0.0003; ORR: 14% vs. 13%). [91] Atezolizumab also showed a better safety profile compared to docetaxel (≥ 3 TRAE:15% vs. 43%).

1.8 Treatment patterns, outcomes, and healthcare utilization and costs in patients with advanced/metastatic NSCLC

In this section, the literature regarding treatment patterns, treatment outcomes, healthcare utilization, and costs in patients with lung cancer using claims data, EMR data, and cancer registry data will be discussed.

1.8.1 Treatment patterns

Trends in systemic treatment utilization

Although clinical trials have demonstrated that chemotherapy could improve survival and quality of life, real-world claims studies showed that chemotherapy is underutilized among patients with advanced/metastatic NSCLC. [92, 93, 94, 95, 96, 97, 98, 99, 100, 101] SEER-Medicare-based studies found that the rate of receipt of first-line chemotherapy was only 20% to 31% in elderly patients with advanced/metastatic NSCLC. [92, 93, 94, 96] Considering second- and third-line treatment, chemotherapy was used in 45% to 60% of US Medicare enrollees with advanced/metastatic NSCLC. [96, 102] Rates of chemotherapy receipt in other countries such as Canada, Netherlands, and South Korea were higher than that reported in the U.S, but still did not exceed 50%. [99, 100, 101] Physicians may be hesitant to use chemotherapy because of patient intolerance to the toxicity of chemotherapy. Other reasons for not treating with chemotherapy may be poor PS, and patients' and physicians' preferences. [98, 103]

SEER-Medicare-based studies only captured elderly patients receiving care from fee-for-service settings. However, rates of chemotherapy receipt may differ in younger patients and those receiving care outside of fee-for-service settings. [98] Compared to elderly patients (≥ 65 years), a greater percentage of younger patients with advanced/metastatic NSCLC received chemotherapy

(18.8% vs. 5.1%, $P < 0.001$) and 4% to 8% of them received chemotherapy as late palliative care (e.g., second-line treatment) according to commercial insurance claims from Virginia Blue Cross and Blue Shield. Ritzwoller and colleagues found that first-line chemotherapy was used more often (54.6%) in health maintenance organizations (HMOs) compared to results reported in published studies using SEER-Medicare data, and younger patients (< 65) were more likely than older patients to receive first-line chemotherapy (68% vs 46%). [95]

Studies revealed an increasing trend of chemotherapy use over time. [92, 93, 95, 104, 105] The increasing trend of chemotherapy use reported in studies may be due to the increasing prevalence of advanced NSCLC and advances in treatment for NSCLC over the years. Using the SEER-Medicare database, Ramsey et al. found chemotherapy use rose from 21% to 43% between 1994 and 1999. The greatest increases were for the use of platinum-taxane regimens (docetaxel/paclitaxel). Patients were less likely to receive platin plus a nontaxane agent [92]. Lang et al. reported a moderate increase in utilization of first-line chemotherapy from 1997 to 2002 (28% vs 36%) among Medicare enrollees. [93] Use of both doublets and single agents increased across study years, which reflected a general increase in chemotherapy use. Regarding specific chemotherapy regimens, use of gemcitabine-containing doublets increased substantially from 0.3% among those diagnosed in 1997 to 12% among those diagnosed in 2002. Consistent with studies using the SEER-Medicare data, chemotherapy use increased significantly from 51% in 2000 to 59% in 2007 among patients in HMOs. [95] However, unlike the SEER-Medicare-based studies, doublet therapy utilization decreased in HMOs from 87% to 65% over the study years (2000-2007), while single therapy utilization increased from 12% to 23% between 2000 and 2004.

The emergence of third-generation chemotherapy (e.g., docetaxel and pemetrexed) and targeted therapy (e.g., erlotinib and gefitinib) approved in the past 2 decades has changed the

management of NSCLC. One striking finding was that the use of carboplatin-paclitaxel-bevacizumab and erlotinib as first-line treatments increased after 2005, although carboplatin-paclitaxel-bevacizumab was approved as first-line treatment for advanced NSCLC in 2006 and erlotinib was approved as maintenance treatment after four cycles of platinum-based first-line chemotherapy for advanced NSCLC patients in 2007. This may indicate these drugs were used off-label. In contrast to the increasing use of erlotinib after its FDA approval, the use of gefitinib stopped after the FDA withdrew it from the market. [105] Gefitinib received accelerated approval in 2003 for the treatment of patients with advanced NSCLC after progression on platinum doublet chemotherapy and docetaxel but was withdrawn from the market since clinical studies suggested it did not improve survival time. The FDA approved gefitinib for the first-line treatment of patients with advanced/metastatic NSCLC with EGFR mutations in 2014.

Distribution of systemic treatment received as first-line treatment and subsequent treatment

Several Medicare-based studies discussed chemotherapy regimens given in first-line and second-line treatment among patients with advanced/metastatic NSCLC. [92, 93, 95, 96, 97, 99, 100, 106] In general, these studies included patients who were over 65 years of age, continuously enrolled in Medicare Part A and Part B, and had no other cancers or surgical resection.

A study by Ramsey found that first-line chemotherapy use presented a homogeneous pattern between 1994 and 1999. [92] Approximately one-third of patients received doublet therapy with cisplatin or carboplatin plus paclitaxel or docetaxel, one-third received cisplatin or carboplatin plus a nontaxane agent, and one-third received single-agent therapy or a doublet that did not include cisplatin or carboplatin. Very few patients received single-agent therapy with cisplatin or carboplatin alone.

Davidoff et al. reported the distribution of chemotherapy given as first-line and second-line treatments among Medicare enrollees with advanced/metastatic NSCLC between 1997 and 2002. [96] Among patients who received first-line chemotherapy, about half of the patients received a platinum-taxane regimen (48%), followed by 23.3% receiving single agents, 19% receiving platinum-other regimens, 6% receiving doublet regimens without platinum, and the remaining 5% receiving other treatments. In another words, two-thirds of patients with chemotherapy received a platinum-doublet regimen. Among patients receiving second-line therapy, 63% received a single agent, 23% received platinum doublets and the remaining 14% received doublets without platinum. The study showed that single agents dominated in second-line treatment. The most frequently used single agents were gemcitabine (31%) and docetaxel (32%). Lang et al. echoed the study by Davidoff et al. in which docetaxel/paclitaxel were the most frequently used taxane regimens in addition to platinum from 1997 to 2002. [93] Triplets containing vinblastin and mitomycin or taxane and etoposide were not frequently used across the study years.

Using Medicare data from 2000 through 2008, Karve et al. compared chemotherapy use between advanced-stage SCLC patients and metastatic NSCLC patients. More advanced-stage SCLC patients compared to metastatic NSCLC patients used chemotherapy (85.4% vs. 60.3%; $p < 0.001$). [102] Etoposide plus either carboplatin or cisplatin (~73%) and carboplatin plus paclitaxel (65.6%) were most frequently used among advanced-stage SCLC patients and metastatic NSCLC patients, respectively. More advanced-stage SCLC patients were continuously treated with second-line and third-line treatment compared to metastatic NSCLC patients (second-line treatment: 43.2% VS. 22.6%; third-line: 18.0% vs. 8.8%). The most commonly used second-line and third-line regimens were topotecan for advanced-stage SCLC patients (second-line: 26.3%, third-line: 20.8%)

and docetaxel (20.2%) and vinorelbine monotherapy (16.1%) for metastatic NSCLC patients. Regarding growth-factor therapy, erythropoietin (28.4%), darbepoetin (11.9%), and filgrastim (11.4%) were most commonly used for metastatic NSCLC patients.

Davis et al. found similar results using SEER-Medicare data from 2001-2010. [97] Platinum-based doublets were still the most common first-line chemotherapy. Carboplatin-based doublets replaced cisplatin-based doublets, becoming the most frequently used regimens in first-line treatment (carboplatin plus paclitaxel: 45.74%; carboplatin plus gemcitabine: 10.12%; and carboplatin plus docetaxel: 9.32%). However, no evidence supported carboplatin-based regimens as preferred first-line treatment in clinical trial studies. About half of patients initiating first-line chemotherapy switched to a new regimen in second-line treatment. More patients received a single agent as second-line treatment and specific regimens used were varied (gemcitabine: 16.15%; docetaxel: 13.48%; pemetrexed: 11.04%; vinorelbine: 6.08%; paclitaxel: 6.05%; and carboplatin: 3.47%). In third-line treatment, 50% of patients initiating second-line treatment received a new regimen in third-line treatment. Similar to regimens used in second-line treatment, no specific treatment pattern was observed. The most frequently used third-line treatments were gemcitabine (16.35%), carboplatin plus gemcitabine (13.89%), and carboplatin plus paclitaxel (13.37%).

For patients receiving care from HMOs, Ritzwoller et al. compared first-line chemotherapy use between younger patients (<65 years) and older patients (≥ 65 years). [95] Doublet chemotherapy was seen most commonly in first-line treatment for both age groups as in the SEER-Medicare-based studies. Carboplatin-paclitaxel was used most frequently. However, the distribution of chemotherapy use differed between younger patients and older patients. A slightly larger proportion of younger patients received carboplatin-paclitaxel (57.7% vs. 51.1%) or cisplatin-etoposide (7.7% vs. 6.4%), while a slightly smaller proportion of younger patients

received carboplatin-gemcitabine (4.5% vs. 6.1%), carboplatin alone (4.4% vs. 5.1%), carboplatin-docetaxel (2.6% vs. 4.3%), or cisplatin-gemcitabine (2.5% vs. 4.3%). Another difference was seen in use of bevacizumab-carboplatin-paclitaxel. Bevacizumab-carboplatin-paclitaxel was used more frequently in younger patients (4.4%) compared to older patients (1.7%). Approximately equal proportions of younger and older patients received erlotinib (2.3% vs. 2.4%).

A recently published study compared first-line chemotherapy regimens among patients from an integrated health care system, Kaiser Permanente California. [106] This study included patients who were over 18 years of age and had initial treatment for stage IIIB or stage IV NSCLC after a diagnosis of NSCLC from 2008 to 2013. About half of patients used platinum doublets (52.3%). Among these patients receiving platinum doublets, carboplatin plus paclitaxel was used most frequently (35.5%), followed by carboplatin plus gemcitabine (15.7%). Cisplatin-based doublets were used less frequently probably due to toxicity concerns. Pemetrexed-based regimens were used by 13.4%. Less than 10% of patients received bevacizumab-based regimens (8.0%), followed by singlets (5.5%), and pemetrexed and bevacizumab-based combinations (1.8%). Utilization of oral tyrosine-kinase inhibitors (TKIs), including erlotinib, gefitinib, afatinib, crizotinib, ceritinib, and alectinib, was relatively high (19.0%) in this study due to the longer and more recent study period.

A study by Carpentier et al. compared modern chemotherapy (vinorelbine, gemcitabine, paclitaxel, docetaxel, and pemetrexed) and targeted therapy (gefitinib and erlotinib) use over the 1998 to 2001 and 2002 to 2005 periods. [107] Platinum-based chemotherapy was most frequently used in first-line treatment, with an increase in carboplatin administration and a decrease in cisplatin administration. Third-generation chemotherapy with/without a platinum accounted for 89.6% and 98% over the 1998 to 2001 and 2002 to 2005 periods, respectively. Targeted therapy was

rarely used in first-line treatment in either study period. About half of patients used second-line therapy. Among those patients, 86.2% of patients received third-generation chemotherapy with/without a platin and 11.9% of patients received targeted therapy during the study period of 2002-2005. For patients receiving third-line treatment (26.2%), targeted therapy became more commonly prescribed. Nearly half (47.1%) of these patients received targeted therapy as third-line treatment.

Nadler et al. evaluated treatment patterns of chemotherapy, targeted therapy and immunotherapy in metastatic NSCLC patients using the US Oncology Network iKnowMed (iKM) electronic health record (EHR) from 2012 to 2016. [108] Chemotherapy was predominant in first-line treatment (93%); carboplatin with paclitaxel (37%), carboplatin with pemetrexed (21%), and bevacizumab with paclitaxel and bevacizumab (13%) were the most frequently used chemotherapies in this group. Targeted therapy accounted for only 6% in first-line treatment with 3.7% and 0.8% patients receiving erlotinib and crizotinib, respectively. Higher rates of use of targeted therapy and immunotherapy were observed in second-line treatment and third-line treatment, which could be explained by the preferred use of some of the targeted therapies during disease progression after platinum-based treatment. Of the patients who received first-line treatment, 40% progressed to second-line treatment. Among these patients, 66% of patients received chemotherapy, 17% received immunotherapy, and 17% received targeted therapy. Pemetrexed (16%) and docetaxel (16%) were the most frequently used second-line chemotherapy, erlotinib (11%) was the most frequently used second-line targeted therapy, and nivolumab (16%) was the most frequently used second-line immunotherapy. In third-line treatment, although most people received chemotherapy, nivolumab was the most commonly used regimen (17%). The study also found that most patients stayed in the same treatment group while moving to the

subsequent treatment; however, a small proportion of patients receiving targeted therapy as second-line treatment switched to chemotherapy as third-line treatment (18%).

In order to understand contemporary treatment patterns and outcomes for patients with advanced NSCLC, a global retrospective study (the PivOTAL study) was conducted at academic and community oncology centers in nine countries (Europe, Asia, Australia, and North and South America) from January 2011 to May 2016. [109] Patient demographic characteristics were similar across countries except for race. Platinum-based therapy was the most common first-line therapy except for Taiwan. Platinum-based therapy use was lowest in Taiwan (17%) and highest in Brazil (92%), with inconsistent use patterns of carboplatin-based and cisplatin-based therapy. Targeted therapy accounted for a high proportion of first-line treatment in Asian countries [Taiwan (55%) and Korea (22%)], while its use was still low in other countries ($\leq 10\%$). In general, over half of patients progressed to second-line treatment. Single agents were the most common second-line therapies in Italy (49%), Spain (43%), Germany (29%), Australia (60%), and Brazil (72%). Platinum-based therapy and single-agent therapy were used equally (31%) as second-line treatment in Taiwan. Targeted therapy administration greatly increased in second-line treatment in each country (20%-30%) except for Taiwan in which the rate of targeted therapy dropped to 19%. Targeted therapy (54%) dominated in second-line therapy in Korea, followed by single-agent therapy (32%). The percent of patients receiving third-line treatment ranged from 17% (Brazil) to 42% (Taiwan). Single-agent and targeted therapies were the most commonly used third-line treatments in all countries.

Findings from Japan were reported in a separate study. [110] This study reviewed medical record data of patients with newly diagnosed advanced/metastatic NSCLC in Japan from 2011 to 2013. Similar to the results of the PivOTAL study, platinum-based therapy (66%) was dominant

in first-line treatment. However, compared to western countries, targeted therapy was used in a greater proportion of patients (25%) in Japan. Over half of patients (60%) progressed to second-line treatment. Among these patients, 49% received single agents, 29% received platinum-based therapy, and 21% received targeted therapy. Docetaxel and erlotinib were the most common single-agent and targeted therapies, respectively. Of the patients who received second-line therapy, 51% progressed to third-line treatment. Of those patients in third-line treatment, 44% of patients received single agents with pemetrexed most commonly used. Platinum-based therapy (22%) and targeted therapy (24%) were used nearly equally. Erlotinib was the only targeted therapy in third-line treatment. According to the PivOTAL study, targeted therapy tended to be more common in Asian countries.

To assess concordance with NCCN guidelines for patients with advanced/metastatic NSCLC, Zornosa et al. used the NCCN NSCLC Outcomes Database to report first-line systemic therapy practice patterns. [111] The analysis included patients who were diagnosed with advanced/metastatic NSCLC between September 2006 and November 2009 and received treatment, such as drug therapy, radiation therapy, surgery, or palliative care, at an NCCN-member institution. The study showed that platinum-based doublets (59%) dominated in first-line treatment, followed by single-agent chemotherapy and targeted single agent (21%), and platinum-based doublets combined with a targeted therapy agent (18%). Among platinum-based treatments, carboplatin (87%) was more common compared to cisplatin (13%); however, an increasing administration of cisplatin was observed over the study years (7%, 9%, and 21%), which was driven by increasing use of cisplatin/pemetrexed with/without bevacizumab regimens. As a partner agent combined with a platinum agent, paclitaxel was most common (45%), followed by pemetrexed (24%), docetaxel (15%), and gemcitabine (11%). Bevacizumab and erlotinib were

used by 22% and 1% of patients treated with platinum-based doublets, respectively. Singlets accounted for only 1% of first-line treatment with erlotinib and pemetrexed used most commonly. Generally, 76% of patients received first-line therapy in concordance with NCCN guideline recommendations.

In summary, platin-based doublets are still the main first-line treatment for advanced/metastatic NSCLC, which is consistent with NCCN guidelines. Docetaxel and paclitaxel are commonly used agents with platinum. NCCN guidelines recommend docetaxel, pemetrexed (for non-squamous NSCLC), and erlotinib as standard of care in second-line treatment. Real-world evidence showed a varied distribution of regimens in second-line treatment. Studies have shown that targeted therapies and immunotherapies have been used more as second- and third-line treatment in recent years.

Factors determining receipt of chemotherapy

Previous studies identified several factors associated with the likelihood of receiving chemotherapy in patients with advanced NSCLC. Comparison of study results is difficult given the wide variation in data sources, study populations, study methods, and study years. Patient demographics (age, gender, race, and region), health status (disease stage, comorbidity, and PS), tumor histology (adenocarcinoma and squamous cell), and concurrent treatment (surgery and radiotherapy) were discussed most frequently. [92, 93, 95, 96, 97, 98, 100, 103, 112] In particular, studies indicated that age was a strong determinant of receiving chemotherapy. [92, 93, 96, 97, 98, 100, 103] Patients older than 70 years were 70% less likely to receive chemotherapy compared to younger patients. [100] The likelihood of receiving chemotherapy declines with increasing age.

Patients older than 80 years were about 90% less likely to receive chemotherapy compared to younger patients. [92, 95, 96]

Study results regarding the relationship between gender and receipt of chemotherapy in patients with advanced NSCLC were inconsistent. Some studies showed that females were more likely to receive chemotherapy [92, 96, 100], while other studies found opposite results. [93, 95, 103] Whites were more likely to receive chemotherapy compared to other races/ethnicities. [92, 93, 95, 96, 97] Chemotherapy use varied among regions. [92, 93, 97, 103] Patients living in the South or in rural areas were more likely to receive chemotherapy. Regarding patient health status, patients who were in stage IV NSCLC or had more comorbidities were substantially less likely to receive chemotherapy. [92, 93, 95, 96, 97] PS is an important prognostic factor and is used as a criterion for treatment selection. Patients with better PSs (≤ 2) were more likely to be treated with chemotherapy. [96, 98, 103, 112] NSCLC treatments are determined according to tumor histology, but systematic therapy is typically given regardless of whether the patient has adenocarcinoma or squamous cell carcinoma. Patients with an adenocarcinoma subtype were about 30% more likely to be treated with chemotherapy compared to those with squamous cell carcinoma. [100, 103] A study also indicated that patients who received radiation therapy were more likely to receive chemotherapy, while patients treated with surgery were less likely to receive chemotherapy. [92]

Some of the factors that determine receipt of chemotherapy also affect receipt of a platinum-based doublet. [93, 96] A study by Spence et al. demonstrated the association of patient characteristics and specific regimens received. [106] Patients receiving bevacizumab-based or pemetrexed and bevacizumab-based regimens were younger, and those taking singlets were older and had significantly higher Charlson comorbidity scores. Those receiving a TKI were more likely to be female, Asian, diagnosed at stage IV, have nonsquamous histology, and have never smoked.

Other factors associated with receipt of chemotherapy included tumor size, smoking status, weight loss, education, and income level. [95, 97]

1.8.2 Treatment outcomes

OS, PFS, and ORR are the most commonly used clinical outcome endpoints in claims studies. [105, 94, 96, 97, 98, 99, 106, 103, 104, 112] As shown in clinical trials, systemic treatment in advanced/metastatic NSCLC patients was associated with prolonged OS in claims-based studies. [92, 94, 96, 97, 98, 99, 100, 106, 103, 104] NSCLC treatment-related adverse events (AEs) are used to assess toxicity of systemic treatment and thus, used as a measure of treatment outcome as well. In general, patients with advanced/metastatic NSCLC benefited from receiving systemic treatment. OS was significantly improved in patients receiving systemic treatment when compared to best supportive care alone.

Survival benefit associated with chemotherapy treatments

NSCLC is typically a disease of aging with 47% of patients diagnosed at age 70, but only 25% of patients recruited for clinical trials were 65 and older. Thus, whether elderly patients in real-world practice could achieve the same treatment efficacy as shown in clinical trials was uncertain. The SEER-Medicare data has been used to address this uncertainty. Survival benefits of chemotherapy for older people with advanced/metastatic NSCLC were shown in the Medicare data-based studies. [94, 97, 113]

Davis et al. compared OS among patients with advanced squamous NSCLC who received cancer-directed therapy (surgery, radiation, chemotherapy, or small molecular therapy) and those

who received supportive care only using the SEER-Medicare data from 2001 to 2009. [97] The study found that the median OS was four times longer among patients receiving cancer-directed treatment compared to those receiving supportive care only (median OS: 8 months vs 2 months; $p<0.0001$). However, this study did not specify which treatment contributed to the improvement in OS.

Brooks et al. evaluated 90-day mean hospital-free survival time and OS among Medicare enrollees with NSCLC from 2008 to 2013. [114] The 90-day mean hospital-free survival time was improved for patients receiving carboplatin-pemetrexed therapy (68.4 days) compared to those receiving carboplatin-paclitaxel therapy (63.6 days, $p=0.01$); The median survival time was 9.0 months with carboplatin-pemetrexed therapy compared with 7.6 months with carboplatin-paclitaxel therapy ($p=0.005$). The findings from this study suggest that patients receiving carboplatin-pemetrexed have survival benefits comparable to those receiving carboplatin-paclitaxel.

In another SEER-Medicare analysis by Owonikoko et al., the effectiveness of specific drug treatment was assessed at four time periods soon after the approval of new agents for advanced NSCLC (1988-1994: baseline; 1995-1999: platinum; 1999-2003: docetaxel; 2004-2005: pemetrexed and bevacizumab). [94] During the 1988-1994 period, the survival rates were higher in patients treated with chemotherapy compared to those who were not treated (1-year survival: 32.41% vs. 16.81%; 2-year survival: 14.54% vs. 7.69%; and 5-year survival: 4.26% vs. 2.76%). The median survival time was longer and the risk of death was 34% lower in the chemotherapy group compared with those who were not treated with chemotherapy (median OS: 8 months vs 4 months; HR: 0.66, 95% CI: 0.64-0.68, $P<0.001$). The 1-year survival rate for patients treated with chemotherapy increased from 32.41% in 1988-1994 to 39.55% in 2004-2005, whereas the

improvement for patients not treated with chemotherapy was relatively modest over time, with a growth of 3.61% (1988-1994: 16.81%; 2004-2005: 20.43%). Platinum-based treatment was associated with higher 1-year survival rate (37.47% vs 27.89%), longer OS (9 months vs 6 months), and lower risk of death (HR: 0.78, 95% CI: 0.74-0.83, $P<0.001$) compared to non-platinum chemotherapy. Compared to single-agent platinum therapy, platinum combinations (platinum plus docetaxel, platinum plus vinorelbine, platinum plus gemcitabine, platinum plus paclitaxel, and platinum plus paclitaxel/docetaxel/vinorelbine/gemcitabine) were associated with reduced risk of death. Specifically, docetaxel-, pemetrexed-, and bevacizumab-based therapies showed superior survival in their respective predefined intervals of treatment (Docetaxel: HR: 0.73, 95% CI: 0.70-0.75, $p<0.001$; pemetrexed: HR: 0.4, 95% CI: 0.37-0.44, $p<0.001$; bevacizumab: HR: 0.33, 95% CI: 0.27-0.40, $p<0.001$).

Adding bevacizumab to carboplatin-paclitaxel slightly improved OS in the Medicare population with advanced NSCLC. [113]The median OS was 9.7 months for patients receiving the bevacizumab combination compared with 8.9 months for those receiving carboplatin-paclitaxel in 2006-2007, and 8.0 months for those receiving carboplatin-paclitaxel in 2002-2005; however, bevacizumab was not associated with significant improvement in survival compared to carboplatin-paclitaxel (2006-2007: HR: 1.01, 95% CI: 0.88-1.15; 2002-2005: HR: 0.94, 95% CI: 0.83-1.06).

The SEER-Medicare-based studies favor platinum-based treatments for elderly patients. However, no evidence showed that any specific chemotherapy treatment was superior to others in the Medicare population. A number of studies compared the efficacy of treatment combinations in health care systems other than US Medicare.

Improvement in OS associated with chemotherapy treatments was also reported in a series of studies conducted in Canada. A study using data from the Canada Cancer Registry reported that the median OS was 13.1 months for patients who received chemotherapy compared to 4.2 months for those who received best supportive care. The risk of mortality was significantly lower in the chemotherapy-treated group while controlling for age, sex, ECOG, and histology (HR: 0.68, 95% CI: 0.59–0.78, $p < 0.001$). [150]

Two chart review studies demonstrated that chemotherapy greatly prolonged patients' lives. The first chart review study using data from the Outcome and Surveillance Integrated System (OaSIS) in Canada reported that survival increased over time among patients treated with chemotherapy from 2001 to 2008. [104] The median survival time was 3.5 months for patients receiving best supportive care, 7.9 months for patients receiving first-line chemotherapy, and 17 months for patients receiving second-line chemotherapy ($p < 0.001$). The second chart review study using data from the Ottawa Hospital Cancer Center (2002-2009) indicated that the median OS was 7 months longer among patients who received systemic chemotherapy compared to those who did not receive chemotherapy treatment (median OS: 10.7 vs 3.9 months). The risk of death was about 2 times higher for patients without systemic chemotherapy (HR: 1.80, 95% CI: 1.4-2.3, $p < 0.01$). [98]

In a population-based study in Canada (2005-2009), the median survival times for patients who did not receive chemotherapy, received selected chemotherapy, and received both first-line and second-line chemotherapy were 3.3 months, 8.2 months, and 16.2 months, respectively. [100] For patients receiving first-line treatments, cisplatin-gemcitabine was associated with a lower risk of death compared to carboplatin-gemcitabine (HR: 0.75, 95% CI: 0.65-0.87, $P=0.0001$), and a similar risk of death compared to carboplatin-paclitaxel (HR: 0.97, 95% CI: 0.83-1.14, $P=0.74$)

and carboplatin-vinorelbine (HR: 0.98, 95% CI: 0.79-1.23, P=0.88). Among patients with nonsquamous histology who received either docetaxel or pemetrexed as second-line therapy, pemetrexed was associated with a longer survival time (19.8 months vs. 14.1 months; HR: 0.45, 95% CI: 0.32-0.62; P<0.0001). Disparities in survival outcomes by gender and type of cancer were reported in the study. Females and adenocarcinoma histology were associated with a reduced risk of death compared to males and nonsquamous histology, respectively (Female: HR: 0.80, 95% CI: 0.72-0.89; P<0.0001; adenocarcinoma: HR: 0.80, 95% CI: 0.67-0.95, P=0.01). Surprisingly, younger age was not associated with a better survival outcome.

Survival benefit associated with targeted treatment or immunotherapy

Clinical trials have yielded favored results for EGFRs in patients with confirmed gene mutation. This benefit is comparable with that seen outside of clinical trials. [115, 116, 117, 118, 119] Retrospective studies further confirmed survival benefits in real-world treatment. To compare efficacy of gefitinib and erlotinib, a retrospective study demonstrated that the response rates and disease control rates in the gefitinib-treated and erlotinib-treated groups were comparable (response rate: 76.9% vs 74.4%, P=0.575; disease control: 90.1% vs 86.8%, P=0.305). [116] For patients receiving gefitinib or erlotinib as the first-line treatment, there was no significant difference between the two treatment groups in overall response rates (76.7% and 90.0%, P=0.431) and median PFS (11.7 versus 14.5 months, P=0.507). Similar results were observed in another retrospective study at a Macau government hospital between 2005 and 2015. [117] There was no significant difference in median OS and disease control rates between the gefitinib-treated and

erlotinib-treated groups (OS: 20.2 vs 26.3 months, $P=0.091$; disease control rate: 72.1% vs 81.1%, $P=0.079$). Erlotinib resulted in prolonged PFS (PFS: 11.9 vs 13.4 months, $P=0.016$).

Ceritinib was approved for the treatment of patients with metastatic ALK-positive NSCLC who progress while receiving or are refractory/intolerant to crizotinib in 2014. A chart review study showed that the median PFS for ceritinib was 12.9 months and that 68.6% of patients achieved either a complete or partial response. [118] Gastrointestinal AEs were reported among 17.2% of patients on ceritinib during follow-up, mostly because they were instructed to fast. The authors concluded that ceritinib was effective and tolerated in their study population. Another chart review study in Canada also found that ceritinib was associated with a longer OS compared to patients who did not receive ceritinib (1.7 months vs 20.4 months, $p < 0.001$). [119]

Limited real-world evidence exists regarding the survival outcomes of immunotherapy. [120] Using SEER Medicare linked data, Youn and colleagues examined overall survival of older patients who received nivolumab or pembrolizumab in 2016. The study showed that the median overall survival was 9.3 months (95% CI, 8.5-10.5 months). The 1-year survival rate was 43.0% (95% CI, 40.2-45.7%). The study results were consistent with clinical trial results. [88, 89, 90]

Survival benefit across chemotherapy, targeted therapy, and immunotherapy

Spence et al. estimated survival among therapies used for patients with advanced/metastatic NSCLC in an integrated health care system (2008-2013). [106] Survival analysis showed that the median survival of pemetrexed-bevacizumab-based combinations was 18.5 months, which was longer than survival in the bevacizumab-based regimens (14.5 months), TKI regimens (12.7 months), pemetrexed-based regimens (10.4 months), and platinum-based doublets (9.2 months). Singlets had the shortest median survival at 5.3 months. All treatment

groups were associated with increased survival compared to platinum doublets except for singlets (HR for singlets: 1.5; 95% CI: 1.22-1.84; $P<0.001$). In particular, the risk of death was significantly lower for patients receiving pemetrexed-bevacizumab-based regimens (HR: 0.63, 95% CI: 0.42-0.94 $P=0.023$) or TKIs (HR: 0.84; 95% CI: 0.73-0.94; $P=0.004$) compared to those receiving platinum-based doublets. The result was inconsistent with previous SEER-Medicare-based studies because of different populations and study periods. Subgroup analysis showed that younger patients and patients with nonsquamous histology had similar results; however, only singlets were significantly associated with an increased risk of mortality among elderly patients (HR=1.51; 95% CI=1.20-1.90; $P<0.001$).

In the PlvOTAL study, the OS from first-line treatment ranged from 9.3 months (Brazil) to 25.5 months (Taiwan) regardless of treatment category. [109] The OS was longer in the non-squamous NSCLC subgroup compared to the squamous NSCLC subgroup in most countries (Italy, Spain, Australia, and Taiwan), while OS was similar in the two histological types in Brazil and Korea. The OS from second-line treatment ranged from 5.4 months (Brazil) and 15.8 months (Taiwan) regardless of treatment category. The OS was longer in the non-squamous NSCLC subgroup compared to the squamous NSCLC subgroup across countries except for Brazil. As part of the PlvOTAL study, the study results for Japan were reported separately. [110] The median OS from first-line treatment (9.9 months) and second-line treatment (4.7 months) were slightly lower than the OS observed in other countries in the PLvOTSL report. Consistent with other countries, the non-squamous NSCLC subgroup conferred better survival outcomes. Comparing OS in EGFR/ALK-positive and -negative groups, the EGFR/ALK-positive group achieved superior OS outcomes from the first-line treatment. The median OS for patients with EGFR/ALK-negative status was 6.9 months (95%CI: 5.6-10.0) and 4.0 months (95% CI: 2.8-4.8) from the start of first-

and second-line treatments while that of patients with EGFR/ALK-positive status was 17.9 months (95% CI: 9.9-24.4) and 4.0 months (95% CI: 3.3-12.0), respectively. This result indicated that patients with EGFR/ALK-positive status benefited more from the systemic treatment (chemotherapy and targeted therapy).

A population-based French study found that modern chemotherapy (HR: 0.603; 95% CI: 0.382-0.952) and targeted therapy agents (HR: 0.525; 95% CI: 0.382-0.952) led to a slightly longer survival compared to older agents (P=0.0323). [107] However, the magnitude of the difference was not significant while considering confounders (modern chemotherapy: HR: 0.707; 95% CI: 0.434-1.151; targeted therapy: HR: 0.773; 95% CI: 0.445-1.343; P=0.3708). The study showed good effectiveness of the modern and targeted therapies in advanced NSCLC management. However, TKIs could be used without knowledge of EGFR status during the study period, so the survival benefit of targeted therapy may be underestimated.

A recent published study in 2018 by Nadler et al. provided a good summary of treatment efficacy of current management of advanced/metastatic NSCLC in the US by assessing OS stratified according to line of therapy and treatment category (chemotherapy, targeted therapy and immunotherapy) using US iKM data. [108] Median OSs were 7.2 months, 14.7 months, and 14.7 months for patients who received only first-line treatment, first- and second-line treatment, and first-, second- and third-line treatment, respectively. In first-line treatment, patients who received targeted therapy were observed to have the longest survival (24.3 months) compared to chemotherapy (11.7 months). Similarly, the median OS (11.2 months) was the longest for those who received targeted therapy in second-line treatment. The median OS was 9.7 months for immunotherapy and 9.2 months for chemotherapy. In third-line treatment, patients who received

immunotherapy achieved the longest median OS (11.3 months), followed by chemotherapy (8 months) and targeted therapy (7.4 months).

Dosing change, objective response, toxicity and QOL associated with systemic treatment

Dose change and switching are indicators of potential ineffectiveness of treatment. Little is known about percentages of patients with switching and dose reductions ($\leq 80\%$ of the initial dose) in real-world practice. According to the Care for Outcome (CfO) registry built on the general Dutch Cancer Registry managed by the Netherlands Comprehensive Cancer Organisation (IKNL), about half of patients (52%) received four or more cycles of chemotherapy treatment and 20% of patients had a dose reduction in any line of treatment. [99] Switching to other systematic chemotherapies due to toxicity concerns was found in 15% of patients receiving first-line treatment. Most switching consisted of cisplatin-based regimens, which was consistent with another Canada study. [100] Regarding erlotinib as second-line and third-line treatment, 24% of patients and 29% of patients were identified as having dose reductions and treatment delays during erlotinib treatment, respectively. Treatment delays were due to skin reactions, diarrhea, and fatigue. The most common reasons for discontinuing erlotinib were disease progression (53%), death (22%), and toxicity (11%). However, the study was based on a chart review from 4 community oncology clinics in the US and had a small population of 45 patients. [121]

In a retrospective study in the Netherlands, clinical outcomes were presented over a period of five years (2008–2012). [99] Dose reduction was found in 20% of all study subjects in any line of treatment. Switching to other systemic regimens was found in 15% of all first-line treatments, mostly due to toxicity of cisplatin-based treatment. The median survival time ranged from 276 to 357 days for the systemic chemotherapy group, while the median survival time was much shorter

(50-65 days) for the untreated group. The survival result reported in this study was comparable to previous studies, but no increased survival time was observed over the study years.

Objective response was commonly used in clinical trials to evaluate treatment outcome. A study conducted by the Lung Cancer Group of the Hellenic Oncology Research Group from 1995 to 2000 evaluated objective response to first-line and second-line treatments, as well as OS, among patients with advanced NSCLC. [122] One-third of patients achieved objective response to first-line treatment. For those patients, the median interval between the end of first-line chemotherapy and the initiation of second-line chemotherapy was 2.5 months, while the median interval was 1 month for the nonresponders. For patients receiving second-line treatment, 12.5% of patients achieved objective response, 24.1% exhibited stable disease (SD), and 63.4% exhibited progressive disease (PD). Platinum-based second-line treatment resulted in an objective response of 16.4% compared with 8.8% for nonplatinum-based treatment. Correspondingly, 83.6% of patients receiving platinum-based second-line treatment exhibited SD and PD, while 91.2% of patients receiving nonplatinum-based treatment exhibited SD and PD. The median OS was 13 months and 7 months for patients who received second-line chemotherapy and best supportive care, respectively ($p < 0.001$).

Takeda et al. evaluated PFS and OS according to response rate. The study was a chart-review conducted in two Japanese hospitals. [123] Among 68 patients with EGFR-TKIs, 6 (10%) patients achieved a complete response (CR), 42 (62%) patients achieved a PR, 14 (21%) patients exhibited SD, and 6 (10%) patients had progressive disease (PD). Thus, the response rate (CR+ PR) and disease control rate (CR+ PR + SD) were 71% and 91%, respectively. Analysis of response to EGFR-TKIs treatment revealed that PFS and OS were significantly longer in the CR/PR groups compared to the SD group (PFS: HR: 0.33, 95% CI: 0.17-0.62, $p = 0.001$; OS: HR:

0.29; 95% CI: 0.13-0.68; $p=0.004$). This study indicated that response rate could be an optimal surrogate for survival in patients with EGFR-TKIs.

In selecting the best treatment for patients with advanced/metastatic NSCLC, the balance between symptom relief, survival, and toxicity should be considered. Thus, studies of the toxicity profiles of chemotherapy are valuable. Fifteen AEs were reported during chemotherapy use for advanced NSCLC. Neuropathy, fever with neutropenia, sepsis and neuropathy/febrile neutropenia/sepsis were the most common AEs during chemotherapy. Patients aged 65-74 years old were at the highest risk of developing these AEs. In a large population-based cohort study using the SEER-Medicare data, short-term (<3 months) and long-term (≥ 3 months) chemotherapy-associated toxicities stratified by chemotherapy agent were examined. [124] The most common short-term toxicities included acute anemia (20.0-35.9%), nausea (20.1-60.0%), and neutropenia (9.2-22.5%). Unlike short-term toxicities, there was more variability in long-term toxicities. The most common long-term toxicities included acute anemia (30.7-37.6%), dehydration (24.9-33.6%), respiratory failure (26.3-40.8%), pulmonary fibrosis (25.0-33.3%), neutropenia (17.0-33.3%), nausea (16.0-25.6%), and fever (13.3-20.0%). Additionally, the risk of developing ischemic heart disease, conduction disorders, cardiac dysfunction, and heart failure increased with use of chemotherapy among elderly people with advanced NSCLC. [125]

Regarding erlotinib as second- or third-line therapy, patient-reported outcomes showed that nearly half of patients (43.8%) experienced severe fatigue at any time during erlotinib treatment. [121] About one-third of patients had physical pain (34.4%) or shortness of breath (28.1%), and a quarter reported coughing or trouble breathing (21.9%). Other severe symptoms were rash, dry skin, or itching (15.6%), diarrhea (15.6%), and nausea or constipation (6.3%).

Evidence regarding health-related QOL for patients with advanced/metastatic NSCLC is lacking. [121, 126] Sztankay applied the EORTC QLQ-C30 and its lung-cancer specific questionnaire, EORTC QLQ-LC13, to assess health-related QoL among patients with advanced NSCLC in an Australian medical center. The QLQ-C30 includes five domains (physical, role, social, emotional, and cognitive), global QOL, eight symptoms (fatigue, pain, nausea/vomiting, appetite loss, insomnia, dyspnea, diarrhea, and constipation), and financial impact of the disease. The summary score of QLQ-C30 is used as a measure of health-related QOL with a higher score representing a better QoL. The QLQ-LC13 assesses dyspnoea, coughing, haemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, chest pain, arm or shoulder pain, and other pain. There was a significant difference in the QLQ-C30 summary score but not in the specific domains between patients receiving first-line chemotherapy and maintenance therapy (mean: 71.8 vs. 75.7, $P=0.048$). Lower rates of nausea/vomiting, sleep disturbances, appetite loss, and constipation were found during maintenance treatment compared to first-line treatment (nausea/vomiting: 13.5% vs. 8.2%, 95% CI: 1.5%-9.1%, $P=0.006$; sleep disturbances: 39.1% vs. 21.4%, 95% CI: 10.8%-24.7%, $P<0.001$; appetite loss: 26.1% vs. 18.6%, 95% CI: 0.2%-14.7%, $P=0.043$; constipation: 17.3% vs. 10.5%, 95% CI: 1.2%-12.2, $P=0.017$). The improvement in side effects during maintenance treatment could be partially explained by discontinuation of first-line platinum-based treatment.

In summary, the efficacy of chemotherapy in real-world practice was comparable to that seen in clinical trials. First, there was a clear survival benefit associated with receipt of chemotherapy and targeted therapy. Specifically, platinum-based treatment yielded superior benefits. Platinum doublets, compared to singlets, led to better treatment outcomes. Cisplatin/carboplatin plus a taxane was strongly associated with enhanced survival. Second,

targeted therapy and immunotherapy showed good survival outcomes in second- and third-line treatment. Third, patients achieved good response to chemotherapy and improved QOL.

1.8.3 Healthcare utilization and costs

Certainly, lung cancer care is costly and imposes a huge economic burden on patients, their families, and health-care systems. [105, 127] Given the increased prevalence of lung cancer, the advent of new expensive treatments, and improved survival outcomes for NSCLC, it is increasingly necessary to understand the main cost drivers and to select cost-effective treatments.

A number of studies have used real-world data to estimate medical costs for patients with advanced NSCLC. [97, 128, 127, 129, 130, 131, 132] Most studies reported lifetime direct medical care costs using the SEER-Medicare data. However, these studies differed in type of analysis, year of evaluation, care service type, and chemotherapy included.

In a study published in 2015, Davis et al. provided detailed NSCLC-related healthcare utilization and costs by care setting/service type among metastatic squamous NSCLC patients enrolled in the Medicare system. [97] For patients receiving any treatment during available follow-up, 97% had outpatient office/specialist visits with a mean of 28.4 visits per person, 88% had hospital outpatient visits with a mean of 10.5 visits per person, and 87% had inpatient hospital admissions with a mean of 2.4 admissions per person. Mean (SD) total all-cause and NSCLC-related costs per patient during follow-up were \$64,819 (\$56,585) and \$50,701 (\$43,545), respectively. Inpatient hospital admissions were the major driver of total NSCLC-related costs (mean: \$32,247; SD: \$32,318), accounting for 64% of total NSCLC-related costs. Outpatient office/specialist visits accounted for the second highest portion of total NSCLC-related costs (mean: \$14,869; SD: \$22,874), followed by skilled nursing facility admissions (mean: \$10,351;

SD: \$9,997), hospice admissions (mean: \$7,488; SD: \$12,658), other ancillary care visits (mean: \$3,700; SD: \$4,792), and emergency department admissions (mean: \$366; SD: \$378). For the five most common first-line systemic treatment regimens, carboplatin plus docetaxel was most costly (\$4,095 per cycle), followed by carboplatin plus gemcitabine (\$3,249 per cycle), carboplatin plus paclitaxel (\$2,647 per cycle), gemcitabine (\$2,139 per cycle), and cisplatin plus etoposide (\$1,795 per cycle).

Another SEER Medicare study compared costs of four most commonly observed first-line regimens in 2008-2009: paclitaxel/carboplatin, platinum monotherapy, pemetrexed/platinum and paclitaxel/carboplatin/bevacizumab. [133] Monthly Medicare Parts A-B payments per patient were \$7,215 for paclitaxel/carboplatin, \$5,726 for platinum monotherapy, \$5,742 for pemetrexed/platinum, and \$7,352 for paclitaxel/carboplatin/bevacizumab. Considering survival outcomes, paclitaxel/carboplatin/bevacizumab was the most cost-effective treatment.

Using a nationally representative data source, the Medical Expenditure Panel Survey (MEPS), Park et al. estimated 2010-2014 annual health care expenditures per patient with lung cancer. [127] The mean annual expenditures were \$35,141 for all adult lung cancer patients, \$38,247 for those aged 18 to 64 years, and \$33,752 for those ≥ 65 years. By source of payment, private health insurance had the highest mean expenditures (\$21,018) and Medicare had the lowest mean expenditure for patients ≥ 18 . By service type, hospital inpatient and ambulatory care visits accounted for the largest share of expenditures. This study found that younger cancer patients had a relatively higher health care cost burden than elderly cancer patients.

Notably, end-of-life (EOL) cancer care is associated with aggressive care and high costs. In a study by Yabroff et al., the net annualized patient costs for initial, continuing and EOL periods

for Medicare beneficiaries (2007-2013) with lung cancer were \$3,140, \$780, and \$4,003 for Medicare Parts A and B; \$460, \$309, and \$546 for Medicare Part D; \$3,601, \$1,089, and \$4,550 for total costs. [129] Using combined Medicare and MEPS data, the estimated out-of-pocket costs in 2019 for initial, continuing, and EOL periods were \$401, \$416, and \$490 respectively. The total out-of-pocket cost was \$1,353. Lung cancer patients in both age groups (18-64 years and ≥ 65 years) were more likely to have overnight hospitalizations, emergency room visits, ambulatory surgeries, provider office-based or hospital outpatient visits, chemotherapy, and radiation therapy than adults without a cancer history. This finding suggests that decreasing the number or length of these healthcare services could reduce total health costs.

Sheehan et al. assessed cancer-attributable and patient-liability costs using SEER Medicare data (1998-2013). [131] The study reported that cancer-attributable costs for patients who were treated with chemotherapy only at the initial phase were \$8,146 (stage III) and \$6,825 (stage IV) per month for NSCLC, and \$6,347 (limited stage) and \$6,187 (extensive stage) per month for SCLC. Patient-liability costs for patients who were treated with chemotherapy only at the initial phase were \$1,200 (stage III) and \$941 (stage IV) per month for NSCLC, and \$995 (limited stage) and \$768 (extensive stage) per month for SCLC. Compared to the initial treatment phase, the monthly cancer-attributable costs and patient-liability costs for patients who were treated with chemotherapy only at the continuing phase were lower (\$5,756 and \$896 for NSCLC stage III; \$5,104 and \$896 for NSCLC stage IV; \$4,821 and \$637 for SCLC limited stage; \$3,297 and \$647 for SCLC extensive stage). The average monthly cancer-attributable cost for patients treated with chemotherapy at the terminal phase (6 months before death) was highest (\$13,426). Therefore, all three studies suggested that end-of-life care might heavily influence total healthcare costs.

Chen et al. evaluated racial-ethnic disparities in costs and utilization for patients with lung cancer during the EOL (last month) period using the SEER Medicare database (2000-2011). [130] The study found that total EOL costs were significantly higher for all racial-ethnic groups relative to Non-Hispanic (NH) white patients. The relative costs were higher by factors of 1.27 (95% CI, 1.21–1.33) for NH black patients, 1.36 (95% CI, 1.25–1.49) for NH Asian patients, and 1.21 (95% CI, 1.07–1.38) for Hispanic patients among NSCLC patients. Inpatient care costs were the largest component of total end-of-life care costs (NSCLC: 65.5%; SCLC: 65.1%). Regarding hospital costs, ICU costs accounted for the largest proportion. For healthcare utilization, hospital admission rates during the last month of life were significantly higher for all minority groups, while outpatient rates were significantly lower for all minority groups compared with non-Hispanic white patients.

In summary, inpatient hospital admissions were the major driver of lung cancer-related costs. Length of hospitalization, phase of care, stage of disease, patients' age and race/ethnicity might influence total lung cancer-related costs. However, there was no consistent conclusion about which treatment is the most cost-effective. The information about real-world costs of targeted therapy and immunotherapy was limited.

1.9 Study rationale

Several studies reported a trend of increasing use of chemotherapy. [92, 93, 95, 104, 105] Platinum-based doublets were the standard of care for first-line treatment of lung cancer. [8] Docetaxel and paclitaxel were commonly used agents in addition to platinum. However, these studies were published before 2015. The FDA approved a series of oral TKIs, including erlotinib (2013), afatinib (2013), gefitinib (2014), ceritinib (2014), and alectinib (2015), crizotinib (2016), osimertinib (2017), dacomitinib (2018), brigatinib (2020) in recent years. Additionally, three immunotherapies, nivolumab, pembrolizumab and atezolizumab, were approved for the treatment of advanced NSCLC in 2015 and 2016. The introduction of new targeted therapy and immunotherapy has expanded the treatment options for lung cancer management. According to the NCCN guidelines, targeted therapy and immunotherapy are recommended for first-line or second-line therapy for NSCLC (recommendation as category IA). Some of them (such as erlotinib, gefitinib, nivolumab, and pembrolizumab) have now replaced chemotherapy as the first-line treatment.

The literature review revealed several gaps in the literature regarding real-world lung cancer treatment. First, most published studies used outdated data (before 2012) and thus, rarely included newer anticancer drugs. Medicare-based studies did not include oral medications which were covered by Medicare Part D. A few studies using more recent data included some of the targeted therapies. However, these studies were not able to capture the treatment patterns effectively because of data limitations (regional institutional population) and a short study period (follow-up time after introduction of new anticancer agent). The information related to immunotherapy use is also scarce. Only one study compared chemotherapy, targeted therapy, and immunotherapy by treatment line in advanced/metastatic NSCLC patients in the US. [134]

Nivolumab was the only immunotherapy included in the study. The use of immunotherapy to treat NSCLC patients is continuing to expand. Thus, understanding immunotherapy use in current lung cancer treatment is important. While previous studies discussed treatment patterns of chemotherapy, it remains unclear whether the introduction of targeted therapy and immunotherapy greatly changed the type and prevalence of systemic treatment used in lung cancer management.

Second, real-world evidence showed a varied distribution of regimens in subsequent treatments of lung cancer. Targeted therapy and immunotherapy may have a greater influence on second- and third-line treatment because the use of most new agents requires disease progression on platinum-based chemotherapy. However, most previous studies focused on initial treatment only. Little is known about the patterns of treatments after the initial treatment and the switching patterns.

Third, clinical studies tend to include patients who are more likely to benefit from the treatments and thus, certain populations tend to be underrepresented. Claims data could reflect patients' treatment pathways and treatment outcomes in a real-world practice in a broader population group. Considering that lung cancer is a disease of aging, most previous studies chose the SEER Medicare database and assessed treatment patterns and outcomes in the elderly population. Previous studies achieved consistent results showing that survival outcomes were significantly improved among elderly patients receiving systemic treatment. In addition to age, patients' economic status may greatly affect their health behaviors, such as choice of therapy. Low-income lung cancer patients are not well-represented in studies. It is still unclear if treatment patterns and outcomes differ among patients with poor economic status. In contrast to Medicare, Medicaid coverage removes financial barriers to receiving cancer treatment and

increases the likelihood of accessing cancer care. A report by the Cancer Action Network showed that Medicaid is associated with a higher likelihood of receiving preventive care, needed cancer treatment, and better outcomes across a number of different types of cancer, such as breast cancer and colorectal cancer. [135] However, Texas has not expanded Medicaid under the Affordable Care Act (ACA) which means that tobacco cessation and lung cancer screening are not required in Texas Medicaid. The results of studies conducted in states that have expanded Medicaid may not be generalizable to Texas Medicaid enrollees with lung cancer.

Finally, cancer-related healthcare expenditures are consistently high, which causes substantial financial burden for state governments for patients covered by Medicaid. In 2020, cancer treatment costs in Texas were estimated to be almost \$19.6 billion. The cost of treating cancer in Texas paid through Medicaid in 2019 was \$357.4 million. The out-of-pocket cost to cancer patients in Texas in 2019 was approximately \$2.5 billion. [136] Identification of key cost drivers is important for cost containment. Claims-based studies suggested that hospitalization and drug costs drive the cost of treating lung cancer. The ECOG has adopted carboplatin and paclitaxel as the reference regimen since it is associated with fewer nausea events compared to other regimens. However, carboplatin plus paclitaxel costs up to \$12,000 more per treatment course than the least expensive alternative (cisplatin plus vinorelbine) with no better survival outcomes according to a cost-effectiveness study using data from the Southwest Oncology Group Trial S9509. [137] Thus, choice of initial therapy has significant effects on lifetime cancer-attributable costs of care. Treatment associated with fewer hospital visits and shorter length of hospital stay may also help to reduce expenditures. Additionally, the real-world evidence regarding lung cancer-related healthcare utilization and cost among Texas Medicaid enrollees is very limited. A few studies using claims data did not report healthcare utilization and costs at the

patient level or consider different follow-up times, so it is hard to determine which regimens are more costly or which regimens offer equivalent outcomes at a lower cost in clinical practice.

In summary, studies regarding actual practice treatment patterns, and healthcare utilization and costs in patients with lung cancer in the US are needed. Previous studies rarely compared traditional systemic chemotherapy and newer targeted treatments and immunotherapy. Using the latest available data from the Texas Medicaid database, this proposed study will contribute to the literature in three important ways. First, it updates the information regarding new regimens used in more recent clinical practice for the Texas Medicaid population with lung cancer. The study will include traditional chemotherapy, as well as targeted therapy and immunotherapy. This study will provide a broader perspective on initial and subsequent treatments received across treatment groups. Second, this study will help to understand treatment patterns among patients with low economic status who are underrepresented in previous literature. Third, this study will provide important information about lung cancer-related healthcare resource utilization and costs on a patient-level basis. The study will help to identify the important cost drivers in real-world clinical practice.

1.10 Study objectives and hypotheses

The objectives of this study and their related hypotheses are:

1. To describe and compare demographic characteristics (age, gender, race/ethnicity, and urban/rural status) and Charlson Comorbidity Index (CCI) scores of the study sample across treatment groups (chemotherapy, targeted therapy, and immunotherapy).

H₀1a: There are no significant differences in **age** across treatment groups;

H₀1b: There are no significant differences in **gender** across treatment groups;

H₀1c: There are no significant differences in **race/ethnicity** across treatment groups;

H₀1d: There are no significant differences in **urban/rural status** across treatment groups;

H₀1e: There are no significant differences in **CCI groups** across treatment groups.

2. To describe and compare treatment patterns in terms of treatment groups and treatment regimens (e.g., platinum-taxane doublet, platinum-nontaxane doublet, triplet therapy with platinum, single targeted therapy, singlet immunotherapy etc.) by treatment line (initial and subsequent treatment).

H₀2a: There are no significant differences in proportions of patients in **treatment groups** by treatment line;

H₀2b: There are no significant differences in proportions of patients receiving different **treatment regimens** (including chemotherapy regimens, targeted therapy regimens and immunotherapy regimens) by treatment line;

H₀2c: There are no significant differences in proportions of patients receiving **chemotherapy regimens** by treatment line;

H₀2d: There are no significant differences in proportions of patients receiving **targeted therapy regimens** by treatment line;

H₀2e: There are no significant differences in proportions of patients receiving **immunotherapy regimens** by treatment line;

3. To compare **lung cancer-related healthcare utilization** among lung cancer patients in terms of hospitalizations, inpatient hospital days, ED visits, office visits, hospital

outpatient visits, home visits, and other visits by **treatment group**, while controlling for covariates.

H₀3a-b: There are no significant differences in the number of **lung cancer-related hospitalizations** for the immunotherapy (a) and targeted therapy (b) groups compared to the chemotherapy group, while controlling for covariates;

H₀3c-d: There are no significant differences in the number of **lung cancer-related inpatient hospital days** for the immunotherapy (c) and targeted therapy (d) groups compared to the chemotherapy group, while controlling for covariates;

H₀3e-f: There are no significant differences in the number of **lung cancer-related ED visits** for the immunotherapy (e) and targeted therapy (f) groups compared to the chemotherapy group, while controlling for covariates;

H₀3g-h: There are no significant differences in the number of **lung cancer-related office visits** for the immunotherapy (g) and targeted therapy (h) groups compared to the chemotherapy group, while controlling for covariates;

H₀3i-j: There are no significant differences in the number of **lung cancer-related hospital outpatient visits** for the immunotherapy (i) and targeted therapy (j) groups compared to the chemotherapy group, while controlling for covariates;

H₀3k-l: There are no significant differences in the number of **lung cancer-related home visits** for the immunotherapy (k) and targeted therapy (l) groups compared to the chemotherapy group, while controlling for covariates;

H₀3m-n: There are no significant differences in the number of **other lung cancer-related visits** by treatment group, for the immunotherapy (m) and targeted therapy (n) groups compared to the chemotherapy group, while controlling for covariates.

4. To compare **lung cancer-related payment status** (\$0 coded as 0; >\$0 coded as 1) among lung cancer patients in terms of payments for hospitalizations, ED visits, office visit, hospital outpatient visits, home visits, other visits, prescription, and total payments **by treatment group**, while controlling for covariates.

H₀4a-b: There are no significant relationships between **lung cancer-related hospitalization payment status** and treatment group, for the immunotherapy (a) and targeted therapy (b) groups compared to the chemotherapy group, while controlling for covariates;

H₀4c-d: There are no significant relationships between **lung cancer-related ED visit payment status** and treatment group, for the immunotherapy (c) and targeted therapy (d) groups compared to the chemotherapy group, while controlling for covariates;

H₀4e-f: There are no significant relationships between **lung cancer-related office visit payment status** and treatment group, for the immunotherapy (e) and targeted therapy (f) groups compared to the chemotherapy group, while controlling for covariates;

H₀4g-h: There are no significant relationships between **lung cancer-related hospital outpatient visit payment status** and treatment group, for the immunotherapy (g) and targeted therapy (h) groups compared to the chemotherapy group, while controlling for covariates;

H₀4i-j: There are no significant relationships between **lung cancer-related home visit payment status** and treatment group, for the immunotherapy (i) and targeted therapy (j) groups compared to the chemotherapy group, while controlling for covariates;

H₀4k-l: There are no significant relationships between **lung cancer-related other payment status** and treatment group, for the immunotherapy (k) and targeted therapy (l) groups compared to the chemotherapy group, while controlling for covariates.

H₀4m-n: There are no significant relationships between **lung cancer-related prescription payment status** and treatment group, for the immunotherapy (m) and targeted therapy (n) groups compared to the chemotherapy group, while controlling for covariates.

H₀4o-p: There are no significant relationships between **lung cancer-related total payment status** and treatment group, for the immunotherapy (o) and targeted therapy (p) groups compared to the chemotherapy group, while controlling for covariates.

5. To compare **lung cancer-related payments** (>\$0; continuous) among lung cancer patients in terms of payments for hospitalizations, ED visits, office visit, hospital outpatient visits, home visits, other visits, prescription, and total payments **by treatment group**, while controlling for covariates.

H₀5a-b: There are no significant differences in the mean **lung cancer-related hospitalization payments** by treatment group, for the immunotherapy (a) and targeted therapy (b) groups compared to the chemotherapy group, while controlling for covariates;

H₀5c-d: There are no significant differences in the mean **lung cancer-related ED visit payments** by treatment group, for the immunotherapy (c) and targeted therapy (d) groups compared to the chemotherapy group, while controlling for covariates;

H₀5e-f: There are no significant differences in the mean **lung cancer-related office visit payments** by treatment group, for the immunotherapy (e) and targeted therapy (f) groups compared to the chemotherapy group, while controlling for covariates;

H₀5g-h: There are no significant differences in the mean **lung cancer-related hospital outpatient visit payments** by treatment group, for the immunotherapy (g) and targeted therapy (h) groups compared to the chemotherapy group, while controlling for covariates;

H₀5i-j: There are no significant differences in the mean **lung cancer-related home visit payments** by treatment group, for the immunotherapy (i) and targeted therapy (j) groups compared to the chemotherapy group, while controlling for covariates;

H₀5k-l: There are no significant differences in the mean **lung cancer-related other payments** by treatment group, for the immunotherapy (k) and targeted therapy (l) groups compared to the chemotherapy group, while controlling for covariates.

H₀5m-n: There are no significant differences in the mean **lung cancer-related prescription payments** by treatment group, for the immunotherapy (m) and targeted therapy (n) groups compared to the chemotherapy group, while controlling for covariates.

H₀5o-p: There are no significant differences in the mean **lung cancer-related total payments** by treatment group, for the immunotherapy (o) and targeted therapy (p) groups compared to the chemotherapy group, while controlling for covariates.

Chapter 2 Methodology

2.1 Chapter overview

The previous chapter presented the findings from prior studies regarding the treatment patterns, outcomes, healthcare utilization and costs for lung cancer, as well as study objectives and hypotheses for the current study. To meet the objectives, the Texas Medicaid database will be used for analyses. This chapter provides an overview of the data source, study population, study design, variables, and statistical analyses used in this study.

2.2 Data source

This retrospective study utilized a seven and one-half year period (January 1, 2014 – June 30, 2021) of paid medical and prescription claims data from the population of Texas Medicaid enrollees. Texas Medicaid data was selected as the data source for this study for three main reasons:

Firstly, Texas Medicaid is the predominant payer for low-income Texans and those with disabilities, as well as the second largest health insurance provider in terms of coverage of population in Texas. [138] [139] As of April 2021, the Texas Medicaid program served 4.96 million Texans, accounting for 17% of the total population of Texas. Among these covered Texans, enrollees aged 21 and older (including low-income families, the elderly, and the disabled) accounted for 21% of enrollees. [140] These characteristics make Texas Medicaid data useful for studying healthcare for vulnerable subgroups such as minority, low-income, and/or disabled individuals. Unlike a commercial insurance database which typically includes individuals well enough to work, Texas Medicaid enrollees reflect a broader range of health status with many having a lower health status than patients covered by commercial insurance.

Secondly, the Texas Medicaid program provides a set of health benefits specified by federal law and optional health services for certain eligible groups. Texas Medicaid covers healthcare services including doctor and clinic visits, hospital care, emergency services, vaccines, medical equipment and supplies, vision and hearing care, X-rays and lab tests, family planning, pregnancy and childbirth care, mental health treatment, and prescription drugs. [141] Texas Medicaid also covers long-term care services and support for people with disabilities and chronic health problems. Because most enrollees are receiving services from managed care health plans under contract with the state, they have no limit to the number of covered prescriptions per month for enrollees aged <65 years old. Thus, Texas Medicaid could provide a detailed, longitudinal record of utilization, diagnoses, procedures, and prescription utilization.

Thirdly, since information on diagnosis, prescription drug utilization, and associated medical costs are based on provider claims, self-report and nonresponse biases that are common in interview-based studies are avoided.

Data for this study were obtained from the Texas Health and Human Services Commission Medicaid eligibility file, the Texas Medicaid medical service claims database, and the Texas Medicaid paid prescription claims database. The Medicaid eligibility file contains the recipient identification number, date of birth, gender, race/ethnicity, eligibility code, eligibility start date, county code, and plan type. ICD-10 codes in the Texas Medicaid medical service claims were used to identify study subjects with lung cancer-related visits. Lung cancer-related prescription utilization and payment information were retrieved after patients' prescription information was matched with their medical claims using unique identification numbers.

2.3 Study timeline

This study covered a period from 1/1/2014 to 6/30/2021. The index date was defined as the first lung cancer diagnosis date occurring between 7/1/2014 and 6/30/2020 (with no cancer diagnoses occurring during the 6-months prior to the index date). A 6-month pre-index period (6 months before the index diagnosis date) was used to determine whether patients had other cancers prior to the index date. Patients were followed for 12 months after the index date in order to observe utilization of and payments for their medication and other healthcare resources. See Figure 2.1 below for the study timeline.

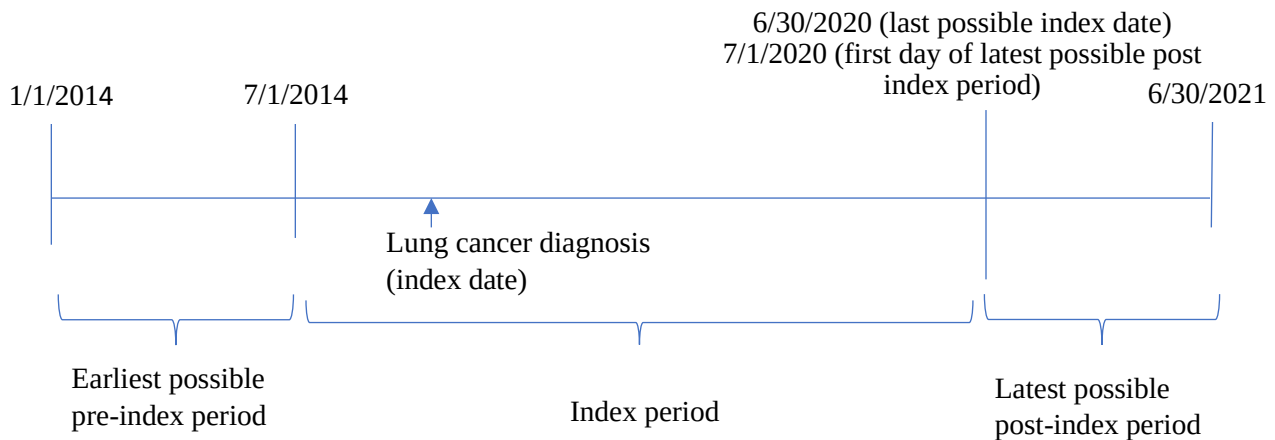


Figure 2.1. Study timeline

2.4 Study population

The main study population consisted of people who were enrolled in Texas Medicaid and diagnosed with lung cancer during the index period. The following criteria were applied to identify the eligible study population.

Patients were included if they:

- (1) were between the ages of 18 and 63 years at the lung cancer index diagnosis date;

- (2) had a diagnosis code for lung cancer (ICD-10-CM: C34.x and C34.xx) as a primary or secondary diagnosis at any point during the index period. The diagnosis date should be the first time a patient is diagnosed with lung cancer. Table 2.1 shows ICD-10 codes used for identifying patients with lung cancer;
- (3) were continuously enrolled in Texas Medicaid during their 6-month pre-index period and 12-month follow-up period. Continuous enrollment will be determined by proxy based on the presence of any Medicaid claim during each quarter of their 18-month observation period (including their 6-month pre-index period and their 12-month follow-up period);
- (4) had ≥ 2 medical visits during 12-month follow-up period; and
- (5) received a treatment recommended by NCCN guidelines for lung cancer.

Table 2.1 ICD-9-CM and ICD-10-CM codes and corresponding descriptions of lung cancer diagnoses

ICD-9	Description	ICD-10	Description
162.2	Malignant neoplasm of main bronchus	C34.00	Malignant neoplasm of unspecified main bronchus
		C34.01	Malignant neoplasm of right main bronchus
		C34.02	Malignant neoplasm of left main bronchus
162.3	Malignant neoplasm of upper lobe, bronchus or lung	C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
		C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
		C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
162.4	Malignant neoplasm of upper lobe, bronchus or lung	C34.2	Malignant neoplasm of middle lobe, bronchus or lung
162.5	Malignant neoplasm of upper lobe, bronchus or lung	C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung

		C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
		C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
162.8	Malignant neoplasm of other parts of bronchus or lung	C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
		C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
		C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
162.9	Malignant neoplasm of bronchus and lung unspecified	C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
		C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
		C34.92	Malignant neoplasm of unspecified part of left bronchus or lung

Source: World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)-WHO Version for; 2016 World Health Organization, 2016, Available at <https://icd.who.int/browse10/2016/en>, February 2022.

Patients were excluded if they:

- (1) had a diagnosis of lung cancer and any other cancers (Table 2.2) during their pre-index period;
- (2) received treatment for SCLC during the pre-index period; or
- (3) were 65 years old or older during the follow-up period.

Table 2.2 ICD-10-CM codes and corresponding descriptions for other cancer diagnoses

ICD-10	Description
C00-C75	Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic, and related tissue
D00-D09	In situ neoplasms
D10-D36	Benign neoplasms
D37-D48	Neoplasms of uncertain or unknown behaviour

Source: World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)-WHO Version for; 2016 World Health Organization, 2016, Accessed at <https://icd.who.int/browse10/2016/en>, February 2022.

2.5 Study design

This retrospective study used the Texas Medicaid medical service claims database and the Texas Medicaid paid prescription claims database. Patient-level data, including date of birth, gender, region, and race/ethnicity were extracted from the Texas Medicaid eligibility file. Continuous enrollment was required since this study quantified and compared lung cancer-related healthcare utilization and payments across different treatment groups at the patient level. Continuous enrollment was defined as patients having Texas Medicaid coverage for at least 6 months before and 12 months after the index date.

2.5.1 Treatment patterns

The distribution of systemic treatments was the main outcome of interest for objective 2. Information pertaining to prescribed lung cancer-related treatment was extracted from the Texas Medicaid prescription claims database (oral medication) and medical claims database (mainly infusions). The number and proportion of patients in each treatment group were reported and compared by treatment line (initial and subsequent). Systemic treatments were classified into 3 groups based on the initial treatment patients received: (1) chemotherapy; (2) targeted therapy (alone and in combination); and (3) immunotherapy (alone and in combination). If a patient received chemotherapy, targeted therapy, and immunotherapy individually, the patient was classified into the corresponding treatment group. If a patient received a targeted therapy in combination with an immunotherapy, the patient was classified into the targeted therapy group. If a patient received an immunotherapy in combination with any other therapy (targeted therapy and/or chemotherapy), the patient was classified into the immunotherapy group.

Initial systemic treatment was defined as the first treatment after the index lung cancer diagnosis date. Additional agents received within 30 days following the day of the first infusion

or fill date were considered to be components of initial treatment if the combined treatment is recommended in the NCCN guideline. A new line of treatment was defined as: (1) a change in regimen (addition of an agent or discontinuation of an agent in a regimen) after a gap of at least 30 days following the end of the previous regimen; or (2) implementation of a different regimen.

Regimens prescribed on same day were considered to be combined treatment if the combination is recommended in the NCCN guideline. Regimens prescribed within a treatment cycle and repeated for several cycles were considered as combined treatment. Information about treatment cycle is summarized in Table 2.3 and Table 2.4. NCCN-recommended therapies were included in this study. Chemotherapy includes platinum agents (e.g., cisplatin, carboplatin), taxanes (paclitaxel, albumin-bound paclitaxel, and docetaxel), vinorelbine, etoposide, pemetrexed and gemcitabine. Targeted therapy includes erlotinib, afatinib, gefitinib, ceritinib, alectinib, crizotinib, osimertinib, bevacizumab and dacomitinib. Immunotherapy includes nivolumab, pembrolizumab, atezolizumab and durvalumab. Chemotherapy agents were further grouped as platinum-taxane doublet regimens, platinum-nontaxane doublet regimens, doublet regimens without platinum, triplet therapy with platinum, cisplatin or carboplatin alone, and other single-agent chemotherapy. Targeted therapy and immunotherapy were grouped based on whether drugs were used in combination (single targeted therapy, doublet/triplet targeted therapy, single immunotherapy, and doublet/triplet immunotherapy).

Table 2.3 Systemic therapy regimens for lung cancer

Systemic therapy regimens	Recommendation
Cisplatin-based chemotherapy	Cisplatin 75mg/m ² , pemetrexed 500mg/m ² day 1, every 21 days
	Cisplatin 75mg/m ² , gemcitabine 1250 mg/m ² days 1 and 8, every 21 days
	Cisplatin 75mg/m ² , docetaxel 75 mg/m ² days 1, every 21 days
	Cisplatin 50mg/m ² day 1 and 8; vinorelbine 25mg/m ² days 1,8,15, and 22, every 28 days
	Cisplatin 100mg/m ² day 1; vinorelbine 30mg/m ² days 1,8,15, and 22, every 28 days
	Cisplatin 75-80mg/m ² day 1; vinorelbine 25-30mg/m ² days 1,8, every 21 days
Carboplatin-based chemotherapy	Carboplatin AUC 6 day 1, paclitaxel 200 mg/m ² day 1, every 21 days
	Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m ² days 1 and 8, every 21 days
	Carboplatin AUC 5 day 1, pemetrexed 500 mg/m ² day 1 for nonsquamous every 21 days

Source: National Comprehensive Cancer Network; NCCL guidelines for patients: Non-small cell lung cancer early and locally advanced; 2021. National Comprehensive Cancer Network 2021. Accessed at www.nccn.org, November 2021

Table 2.4 Targeted therapy or immunotherapy for advanced or metastatic lung cancer

Regimens	Recommendation
Targeted therapy	Afatinib 40 mg orally, once daily
	Erlotinib 150 mg orally, once daily
	Dacomitinib 45 mg orally once daily
	Gefitinib 250 mg orally once daily
	Osimertinib 80 mg orally once daily,
	Erlotinib+ramucirumab, the recommended dose of ramucirumab in combination with erlotinib is 10 mg/kg every 2 weeks
	Erlotinib+bevacizumab, the recommended dose of bevacizumab is 15 mg/kg every 3 weeks
	Ceritinib 750 mg orally once daily
	Alectinib 600 mg orally twice daily.
	Crizotinib 250 mg orally twice daily
	Bevacizumab 15 mg/kg every 3 weeks
Immunotherapy	Nivolumab 3mg/kg or 240mg every 2 weeks
	Pembrolizumab 200mg every 3 weeks or 400 mg every 6 weeks
	Atezolizumab 840mg every 2 weeks or 1200mg every 3 weeks or 1680 mg every 4 weeks
	Durvalumab 10mg/kg every 2 weeks

Source: National Comprehensive Cancer Network; NCCL guidelines for patients: Non-small cell lung cancer early and locally advanced; 2021. National Comprehensive Cancer Network 2021. Accessed at www.nccn.org, November 2021

Specific systemic regimens received were identified using Generic Code Numbers (GCNs) and J-codes. The GCNs and J-codes for chemotherapy, targeted therapy, and immunotherapy included are summarized in Table 2.5 and Table 2.6.

Table 2.5 Generic code numbers of chemotherapy and targeted therapy agents

Name	GCN	Form	Strength
Carboplatin	38450	Vial	150mg/15ml
	8789	Vial	50mg
	8787	Vial	150mg
	8788	Vial	450mg
Cisplatin	8785	Vial	1mg/ml
Paclitaxel	46997	Vial	100mg/16.7ml; 30mg/5ml
Etoposide	8841	Vial	1000mg/50ml; 100mg/5ml; 20mg/ml; 500mg/25ml
	8838	Capsule	50mg
Gemcitabine	25729	Vial	1g
	25728	Vial	200mg
Erlotinib	58375	Tablet	100mg
	58374	Tablet	150mg
	58376	Tablet	25mg
Afatinib	71229	Tablet	20mg
	71230	Tablet	30mg
	71231	Tablet	40mg
Gefitinib	52086	Tablet	250mg
Ceritinib	72296	Tablet	150mg
Alectinib	75271	Capsule	150mg
Crizotinib	67824	Capsule	200mg
	67823	Capsule	250mg
Osimertinib	75146	Tablet	40mg
	75147	Tablet	80mg
Dacomitinib	78998	Tablet	15mg
	78999	Tablet	30mg
	79000	Tablet	45mg

Source: Texas Medicaid records; accessed February 2022.

Table 2.6 J-codes of chemotherapy, targeted therapy and immunotherapy agents

Name	J-code	Form	Strength
Carboplatin	J9045	Vial	50mg
Cisplatin	J9060	Vial	1mg/ml
Paclitaxel	J9267	Vial	1mg
Paclitaxel protein bound	J9264	Vial	1mg
Etoposide	J9181	Vial	10mg
Gemcitabine	J9201	Vial	200mg
Docetaxel	J9171	Vial	10mg/ml; 20mg/ml
Vinorelbine	J9390	Vial	10mg/1ml; 50mg/5ml
Pemetrexed	J9305	Vial	500mg; 100mg
Nivolumab	J9299	Solution	40mg/4ml
Pembrolizumab	J9271	Powder	50mg/vial
Atezolizumab	J9022	Solution	840mg/14ml
Durvalumab	J9173	Vial	500mg/10ml
Bevacizumab	J9035	Vial	400mg/16ml
	Q5107	Vial	400mg/16ml
	Q5118	Vial	400mg/16ml

Source: Oncology Analytics Inc.; HPHC Chemotherapy HCPCS J-Codes List– Prior Authorization Required; accessed February 2022.

2.5.2 Healthcare resource utilization and payments

To address objective 3, lung cancer-related healthcare resource utilization during the 1-year follow-up period was calculated for hospitalizations, inpatient hospital days, ED visits, office visits, hospital outpatient visits, home visits, and other visits. “Other visits” included hospital other, mobile unit, urgent care facility, ambulatory surgical center, skilled nursing facility, nursing facility, custodial care facility, nursing home (skilled nursing facility/intermediate care facility), ambulance-land, ambulance-air or water, independent clinic,

federally qualified health center, psychiatric facility partial facility, independent laboratory, comprehensive inpatient rehabilitation facility, end-stage renal disease treatment facility, state or local public health clinic, rural health clinic, specialty facility (outpatient), other locations, other unlisted facility and unknown. Identification of lung cancer-related healthcare services was accomplished using “place of service” in the Texas Medicaid medical service claims database. The average number of healthcare resource utilization events and length of hospitalization by treatment groups were reported. Healthcare resource utilization was considered lung cancer-related if ICD-10-CM codes C34.X or C34.xx were present in the diagnosis field on the claim.

To address objective 4, lung cancer-related healthcare payments were computed in the 1-year follow-up period using the “payment” variable in the Texas Medicaid service claims database. The mean payments by treatment groups were reported for hospitalizations, ED visits, office visits, hospital outpatient visits, home visits, other visits, prescriptions, and total payments. Drug costs were included in the overall billing during patient visits.

All payments were adjusted using the annual components of the Consumer Price Index to 2021 dollars (most recent data available). [142] Hospitalization payments, ED visit payments, and hospital outpatient payments were adjusted using CPI-hospital services indices. Office visit payments were adjusted using CPI-physician service indices. Prescription payments were adjusted using CPI-prescription indices. Home visit payments and other visit payments were adjusted using CPI-M indices. The CPI-M and specific services indices by year are shown in Table 2.7.

Table 2.7 Annual Components of the Consumer Price Index by year

Year	CPI-M	CPI-hospital services	CPI-physician services	CPI-prescription
2017	475.322	318.170	380.086	519.618
2018	484.707	332.237	380.451	528.008
2019	498.413	338.814	383.228	526.785
2020	518.876	352.952	389.900	532.081
2021	525.276	363.533	406.528	522.392

Source: The Bureau of Labor Statistics: <https://data.bls.gov/cgi-bin/surveymost?cu>. Medical care in the U.S. city average, all urban consumers, not seasonally adjusted

2.6 Study variables

This section describes the independent and dependent variables used in the study.

2.6.1 Independent variables

Demographic characteristics and CCI at baseline

Patient demographic characteristics were measured at the date of diagnosis of lung cancer (index date). Age is a continuous variable defined as the patient's age at the index date. Gender was categorized into female (coded as 0) and male (coded as 1). Race/ethnicity was classified as white (coded as 0), black (coded as 1), Hispanic (coded as 2), and others (American Indian, Asian, and unknown (coded as 3). Urban/rural status was categorized as rural area (coded as 0) and urban area (coded as 1) based on county Metropolitan Statistical Area (MSA) status (Table 2.8).

Table 2.8 Urban/rural status of counties in Texas

Urban/rural status	County name
Urban area (counties in an MSA)	Aransas, Archer, Armstrong, Atascosa, Austin, Bandera, Bastrop, Bell, Bexar, Bowie, Brazoria, Brazos, Burleson, Caldwell, Callahan, Cameron, Carson, Chambers, Clay, Collin, Comal, Coryell, Crosby, Dallas, Denton, Ector, Ellis, El Paso, Falls, Fort Bend, Galveston, Goliad, Grayson, Gregg, Guadalupe, Hardin, Harris, Hays, Hidalgo, Hood, Hudspeth, Hunt, Irion, Jefferson, Johnson, Jones, Kaufman, Kendall, Lampasas, Liberty, Lubbock, Lynn, McLennan, Martin, Medina, Midland, Montgomery, Newton, Nueces, Oldham, Orange, Parker, Potter, Randall, Robertson, Rockwall, Rusk, San Patricio, Smith, Somervell, Tarrant, Taylor, Tom Green, Travis, Upshur, Victoria, Waller, Webb, Wichita, Williamson, Wilson, Wise
Rural area (counties not in an MSA)	Anderson, Andrews, Angelina, Bailey, Baylor, Bee, Blanco, Borden, Bosque, Brewster, Briscoe, Brooks, Brown, Burnet, Calhoun, Camp, Cass, Castro, Cherokee, Childress, Cochran, Coke, Coleman, Collingsworth, Colorado, Comanche, Concho, Cooke, Cottle, Crane, Crockett, Culberson, Dallam, Dawson, Deaf Smith, Delta, DeWitt, Dickens, Dimmit, Donley, Duval, Eastland, Edwards, Erath, Fannin, Fayette, Fisher, Floyd, Foard, Franklin, Freestone, Frio, Gaines, Garza, Gillespie, Glasscock, Gonzales, Gray, Grimes, Hale, Hall, Hamilton, Hansford, Hardeman, Harrison, Hartley, Haskell, Hemphill, Henderson, Hill, Hockley, Hopkins, Houston, Howard, Hutchinson, Jack, Jackson, Jasper, Jeff Davis, Jim Hogg, Jim Wells, Karnes, Kenedy, Kent, Kerr, Kimble, King, Kinney, Kleberg, Knox, Lamar, Lamb, La Salle, Lavaca, Lee, Leon, Limestone, Lipscomb, Live Oak, Llano, Loving, McCulloch, McMullen, Madison, Marion, Mason, Matagorda, Maverick, Menard, Milam, Mills, Mitchell, Montague, Moore, Morris, Motley, Nacogdoches, Navarro, Nolan, Ochiltree, Palo Pinto, Panola, Parmer, Pecos, Polk, Presidio, Rains, Reagan, Real, Red River, Reeves, Refugio, Roberts, Runnels, Sabine, San Augustine, San Jacinto, San Saba, Schleicher, Scurry, Shackelford, Shelby, Sherman, Starr, Stephens, Sterling, Stonewall, Sutton, Swisher, Terrell, Terry, Throckmorton, Titus, Trinity, Tyler, Upton, Uvalde, Val Verde, Van Zandt, Walker, Ward, Washington, Wharton, Wheeler, Wilbarger, Willacy, Winkler, Wood, Yoakum, Young, Zapata, Zavala

Source: Texas Medicaid records; accessed February 2022.

The CCI will be computed over the 6-month pre-index period to obtain a measure of patients' overall baseline comorbidity status. CCI scores were categorized into three groups based on their distribution: 1) without comorbidity (CCI=0, coded as 0); 2) mild comorbidity (CCI=1, coded as 1); and severe comorbidity (CCI>1, coded as 2). Table 2.9 lists disease states and their corresponding weights in calculating the CCI.

Table 2.9 Charlson Comorbidity Index with Deyo adaptations, and corresponding ICD-10 codes

Comorbid Conditions	Weights	Deyo adaptations	ICD-10
Myocardial infarction	1	410-410.9, 412	I21, I22, I252
Congestive heart failure	1	428-428.9	I110, I130, I132, I255, I420, I425-I429, I43, I50, P290
Peripheral vascular disease	1	441-441.9, 443.9, 785.4, V43.4, procedure 38.48	I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959
Cerebrovascular disease	1	430- 438	G45, G46, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69, H340, H341, H342
Dementia	1	290.0-290.9	F00, F01, F02, F03, F04, F05, F061, F068, G132, G138, G30, G310-G312, G914, G94, R4181, R54
Chronic pulmonary disease	1	490-496, 500-505, 506.4	J40-J47, J60-J67, J684, J701, J703, I278, I279
Connective tissue disorder	1	710.0-710.1, 710.4, 714.0-714.2, 714.81, 725	M05, M32, M33, M34, M06, M315, M351, M353, M360
Ulcer disease	1	531-534.9, 531.4-531.7, 532.4-532.7, 533.4-533.7, 534.4-534.7	K25, K26, K27, K28
Mild liver disease	1	571.2, 571.4-571.49, 571.5, 571.6	B18, K700, K701, K702, K703, K709, K713, K714, K715, K717, K73, K74, K760, K762-K764, K768, K769, Z944
Diabetes	1	250-250.3, 250.7	E080, E081, E086, E088, E089, E090, E091, E096, E098, E099, E100, E101, E106, E108, E109, E110, E111, E116, E118, E119
Diabetes with chronic complications	2	250.4-250.6	E102, E112, E132, E142 E103, E113, E133, E143 E104, E114, E134, E144
Hemiplegia or paraplegia	2	342-342.9, 344.1	G041, G114, G800, G801, G802, G81-G83

Moderate or severe renal disease	3	582- 582.9, 583-583.7, 585, 586, 588- 588.9	I120, I1311, I132, N185, N186, N19, N250, Z49, Z992
Moderate or severe liver disease	3	572.2-572.8, 456.0-456.21	I850, I864, K704, K711, K721, K729, K765, K766, K767
AIDS	6	042-044.9	B37, C53, B38, B45, A072, B25, G934, B00, B39, A073, C46, C81-C96, A31, A15-A19, B59, Z8701 A812, A021, B58, R64

Charlson, M.E., et al. (1987) A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. J Chronic Dis, 40(5), pp. 373-383.

Deyo, R.A., et al. (1992) Adapting a Clinical Comorbidity Index for Use with ICD-9-CM Administrative Databases. J Clin Epidemiol, 45(6), pp. 613-619.

Treatment-related variables

Treatment line is a categorical variable which is categorized into initial treatment (coded as 0) and subsequent treatment (coded as 1). Systemic treatment group is the main independent variable for objective 3, objective 4 and objective 5. It is a categorical variable which is categorized as chemotherapy (coded as 0), targeted agents (coded as 1), and immunotherapy (coded as 2).

2.6.2 Dependent variables

Treatment-related variables

In addition to being independent variables as noted above, treatment group and treatment regimens were dependent variables for objective 2 with same definitions as above.

Lung cancer-related healthcare resource utilization- and payment-related dependent variables

Measures for lung cancer-related healthcare resource utilization (hospitalizations and length of stay, ED visits, office visits, hospital outpatient visits, home visits, and other visits) and payments (hospitalization payments, ED visit payments, office visit payments, hospital outpatient visit payments, home visit payments, other payments, prescription payments and total payments) are shown in Table 2.10.

Table 2.10 Healthcare resource utilization- and payment-related dependent variables

Variables	Type	Description/Levels
Lung cancer-related healthcare resource utilization		
Hospitalizations	Count variable	Number of hospitalizations during the post-index period
Inpatient hospital days	Count variable	Number of inpatient hospital days during the post-index period
ED visits	Count variable	Number of ED visits during the post-index period
Office visits	Count variable	Number of office visits during the post-index period
Hospital outpatient visits	Count variable	Number of hospital outpatient visits during the post-index period
Home visits	Count variable	Number of home visits during the post-index period
Other visits	Count variable	Number of other visits during the post-index period
Lung cancer-related payments^a		
Hospitalization payments	Continuous variable	Payments for hospitalizations during the post-index period
ED visit payments	Continuous variable	Payments for ED visits during the post-index period
Office visit payments	Continuous variable	Payments for office visits during the post-index period

Hospital outpatient visit payments	Continuous variable	Payments for hospital outpatient visits during the post-index period
Home visit payments	Continuous variable	Payments for home visits during the post-index period
Other visit payments	Continuous variable	Payments for other visits during the post-index period
Prescription payments	Continuous variable	Payments for prescriptions during the post-index period
Total health care payments	Continuous variable	Payments for all medications and services during the post-index period

^a Payment variables were dichotomized (\$0 coded 0, and >\$0 coded 1) for objective 4 analyses.

2.7 Statistical analysis

Frequencies and histograms were used to examine distributions of variables and to check for outliers. These results were used to determine appropriate inferential tests. For objective 1, descriptive statistics, chi-square tests for categorical variables, and ANOVA for age were used to compare demographic characteristics across treatment groups. For objective 2, descriptive statistics and chi-square tests were used to compare treatment patterns in terms of treatment groups and treatment regimens by treatment line. To compare lung cancer-related healthcare resource utilization measured as count variables across systemic treatment groups (objective 3), zero-inflated negative binomial models were used. To compare lung cancer-related healthcare resource payments across systemic treatment groups (objectives 4 and 5), hurdle models consisting of logistic regressions for the dichotomized payment variables followed by generalized linear models (GLM) with a gamma distribution and a log link function were used for all payment variables except prescription payments. The analysis for prescription payments could not be conducted because a small number of patients had claims for medications of interest.

The analysis for total payments used only the GLM model because all patients with healthcare visits had payments > \$0. Statistical Analysis System (SAS) version 9.4 was used for data analysis. All analyses were two-tailed and the alpha level of significance was set at $p < 0.05$. Table 2.11 shows the statistical tests conducted for each objective and hypothesis in this study.

Table 2.11 Study objectives, hypotheses, and statistical analyses

Objectives/hypotheses	Dependent variables (type)	Independent variables (type)	Statistical analyses
Objective 1. To describe and compare demographic variables (age, gender, race/ethnicity, and urban/rural status) and CCI of the study sample across treatment groups (chemotherapy, targeted therapy, and immunotherapy).			
H ₀ 1a: There are no significant differences in age across treatment groups	Age (continuous)	Treatment groups (categorical)	Descriptive statistics and ANOVA test
H ₀ 1b: There are no significant differences in gender across treatment groups	Gender (categorical)	Treatment groups (categorical)	Descriptive statistics and chi-square test
H ₀ 1c: There are no significant differences in race/ethnicity across treatment groups	Race/Ethnicity (categorical)	Treatment groups (categorical)	Descriptive statistics and chi-square test
H ₀ 1d: There are no significant differences in urban/rural status across treatment groups	Urban/rural (categorical)	Treatment groups (categorical)	Descriptive statistics and chi-square test
H ₀ 1d: There are no significant differences in CCI groups across treatment groups	CCI groups (categorical)	Treatment groups (categorical)	Descriptive statistics and chi-square test
Objective 2. To describe and compare treatment patterns in terms of treatment groups and treatment regimens (e.g., platinum-taxane doublet, platinum-nontaxane doublet, triplet therapy with platinum, single targeted therapy, singlet immunotherapy etc.) by treatment line (first and subsequent treatment).			
H ₀ 2a: There are no significant differences in proportions of patients in treatment groups by treatment line	Treatment groups (categorical)	Treatment lines (categorical)	Descriptive statistics and chi-square test
H ₀ 2b: There are no significant differences in proportions of	Treatment regimens (categorical)	Treatment lines (categorical)	Descriptive statistics and chi-square test

Objectives/hypotheses	Dependent variables (type)	Independent variables (type)	Statistical analyses
patients receiving treatment regimens (including chemotherapy regimens, targeted therapy regimens and immunotherapy regimens) by treatment line			
H ₀ 2c: There are no significant differences in proportions of patients receiving chemotherapy regimens by treatment line	Chemotherapy regimens (categorical)	Treatment lines (categorical)	Descriptive statistics and chi-square test
H ₀ 2d: There are no significant differences in proportions of patients receiving targeted therapy regimens by treatment line	Targeted therapy regimens (categorical)	Treatment lines (categorical)	Descriptive statistics and chi-square test
H ₀ 2e: There are no significant differences in proportions of patients receiving immunotherapy regimens by treatment line	Immunotherapy regimens	Treatment lines (categorical)	Descriptive statistics and chi-square test
Objective 3. To compare lung cancer-related healthcare utilization among lung cancer patients in terms of hospitalizations, inpatient hospital days, ED visits, office visits, hospital outpatient visits, home visits, and other visits by treatment group, while controlling for covariates.			
H ₀ 3a-b: There are no significant differences in the number of lung cancer-related hospitalizations for the immunotherapy (a) and targeted therapy (b) groups compared to the chemotherapy group, while controlling for covariates ^a	Number of lung cancer-related hospitalizations (count)	Treatment groups (categorical) covariates	Zero-Inflated Negative Binomial models
H ₀ 3c-d: There are no significant differences in the number of lung	Number of lung cancer-related inpatient hospital days (count)	Treatment groups (categorical) covariates	Zero-Inflated Negative Binomial models

Objectives/hypotheses	Dependent variables (type)	Independent variables (type)	Statistical analyses
cancer-related inpatient hospital days for the immunotherapy (c) and targeted therapy (d) groups compared to the chemotherapy group , while controlling for covariates ^a			
H ₀ 3e-f: There are no significant differences in the number of lung cancer-related ED visits for the immunotherapy (e) and targeted therapy (f) groups compared to the chemotherapy group , while controlling for covariates ^a	Number of lung cancer-related ED visits (count)	Treatment groups (categorical) covariates	Zero-Inflated Negative Binomial models
H ₀ 3g-h: There are no significant differences in the number of lung cancer-related office visits for the immunotherapy (g) and targeted therapy (h) groups compared to the chemotherapy group , while controlling for covariates ^a	Number of lung cancer-related office visits (count)	Treatment groups (categorical) covariates	Zero-Inflated Negative Binomial models
H ₀ 3i-j: There are no significant differences in the number of lung cancer-related hospital outpatient visits for the immunotherapy (i) and targeted therapy (j) groups compared to the chemotherapy group , while controlling for covariates ^a	Number of lung cancer-related hospital outpatient visits (count)	Treatment groups (categorical) covariates	Zero-Inflated Negative Binomial models

Objectives/hypotheses	Dependent variables (type)	Independent variables (type)	Statistical analyses
H ₀ 3k-l: There are no significant differences in the number of lung cancer-related home visits for the immunotherapy (k) and targeted therapy (l) groups compared to the chemotherapy group , while controlling for covariates	Number of lung cancer-related home visits (count)	Treatment groups (categorical) covariates	Zero-Inflated Negative Binomial models
H ₀ 3m-n: There are no significant differences in the number of lung cancer-related other visits for the immunotherapy (m) and targeted therapy (n) groups compared to the chemotherapy group , while controlling for covariates	Number of lung cancer-related other visits (count)	Treatment groups (categorical) covariates	Zero-Inflated Negative Binomial models
Objective 4. To compare lung cancer-related payment status (\$0 coded as 0; >\$0 coded as 1) among lung cancer patients in terms of payments for hospitalizations, ED visits, office visits, hospital outpatient visits, home visits, other visits, prescriptions, and total payments by treatment group, while controlling for covariates.			
H ₀ 4a-b: There are no significant relationships between lung cancer-related hospitalization payment status and treatment group , for the immunotherapy (a) and targeted therapy (b) groups compared to the chemotherapy group , while controlling for covariates ^a	Lung cancer-related hospitalization payment status (dichotomous)	Treatment groups (categorical) covariates	Hurdle model: logistic regression
H ₀ 4c-d: There are no significant relationships between lung cancer-related ED visit payment status and treatment group , for the immunotherapy	Lung cancer-related ED visit payment status (dichotomous)	Treatment groups (categorical) covariates	Hurdle model: logistic regression

Objectives/hypotheses	Dependent variables (type)	Independent variables (type)	Statistical analyses
(c) and targeted therapy (d) groups compared to the chemotherapy group, while controlling for covariates ^a			
H ₀ 4e-f: There are no significant relationships between lung cancer-related office visit payment status and treatment group , for the immunotherapy (e) and targeted therapy (f) groups compared to the chemotherapy group, while controlling for covariates ^a	Lung cancer-related office visit payment status (dichotomous)	Treatment groups (categorical) covariates	Hurdle model: logistic regression
H ₀ 4g-h: There are no significant relationships between lung cancer-related hospital outpatient visit payment status and treatment group , for the immunotherapy (g) and targeted therapy (h) groups compared to the chemotherapy group, while controlling for covariates ^a	Lung cancer-related hospital outpatient visit payment status (dichotomous)	Treatment groups (categorical) covariates	Hurdle model: logistic regression
H ₀ 4i-j: There are no significant relationships between lung cancer-related home visit payment status and treatment group , for the immunotherapy (i) and targeted therapy (j) groups compared to the chemotherapy group, while controlling for covariates ^a	Lung cancer-related home visit payment status (dichotomous)	Treatment groups (categorical) covariates	Hurdle model: logistic regression

Objectives/hypotheses	Dependent variables (type)	Independent variables (type)	Statistical analyses
H ₀ 4k-l: There are no significant relationships between lung cancer-related other visit payment status and treatment group , for the immunotherapy (k) and targeted therapy (l) groups compared to the chemotherapy group , while controlling for covariates ^a	Lung cancer-related other visit payment status (dichotomous)	Treatment groups (categorical) covariates	Hurdle model: logistic regression
H ₀ 4m-n: There are no significant relationships between lung cancer-related prescription payment status and treatment group , for the immunotherapy (m) and targeted therapy (n) groups compared to the chemotherapy group , while controlling for covariates ^a	Lung cancer-related prescription payment status (dichotomous)	Treatment groups (categorical) covariates	Hurdle model: logistic regression
H ₀ 4o-p: There are no significant relationships between lung cancer-related total payment status and treatment group , for the immunotherapy (o) and targeted therapy (p) groups compared to the chemotherapy group , while controlling for covariates ^a	Lung cancer-related total payment status (dichotomous)	Treatment groups (categorical) covariates	Hurdle model: logistic regression
Objective 5. To compare lung cancer-related payments (>\$0; continuous) among lung cancer patients in terms of payments for hospitalizations, ED visits, office visit, hospital outpatient visits, home visits, other visits, prescription and total payments by treatment group, while controlling for covariates.			
H ₀ 5a-b: There are no significant differences in the mean lung cancer-related hospitalization	Mean lung cancer-related hospitalization payment (continuous) covariates	Treatment groups (categorical) covariates	Hurdle model: GLM with a gamma distribution and a log link

Objectives/hypotheses	Dependent variables (type)	Independent variables (type)	Statistical analyses
payments by treatment group , for the immunotherapy (a) and targeted therapy (b) groups compared to the chemotherapy group , while controlling for covariates ^a			
H ₀ 5c-d: There are no significant differences in the mean lung cancer-related ED visit payments by treatment group , for the immunotherapy (c) and targeted therapy (d) groups compared to the chemotherapy group , while controlling for covariates ^a	Mean lung cancer-related ED visit payment (continuous) covariates	Treatment groups (categorical) covariates	Hurdle model: GLM with a gamma distribution and a log link
H ₀ 5e-f: There are no significant differences in the mean lung cancer-related office visit payments by treatment group , for the immunotherapy (e) and targeted therapy (f) groups compared to the chemotherapy group , while controlling for covariates ^a	Mean lung cancer-related office visit payment (continuous) covariates	Treatment groups (categorical) covariates	Hurdle model: GLM with a gamma distribution and a log link
H ₀ 5g-h: There are no significant differences in the mean lung cancer-related hospital outpatient visit payments by treatment group , for the immunotherapy (g) and targeted therapy (h) groups compared to the chemotherapy group ,	Mean lung cancer-related hospital outpatient payment (continuous) covariates	Treatment groups (categorical) covariates	Hurdle model: GLM with a gamma distribution and a log link

Objectives/hypotheses	Dependent variables (type)	Independent variables (type)	Statistical analyses
while controlling for covariates			
H ₀ 5i-j: There are no significant differences in the mean lung cancer-related home visit payments by treatment group , for the immunotherapy (i) and targeted therapy (j) groups compared to the chemotherapy group , while controlling for covariates ^a	Mean lung cancer-related home visit payment (continuous) covariates	Treatment groups (categorical) covariates	Hurdle model: GLM with a gamma distribution and a log link
H ₀ 5k-l: There are no significant differences in the mean lung cancer-related other visit payments by treatment group , for the immunotherapy (k) and targeted therapy (l) groups compared to the chemotherapy group , while controlling for covariates ^a	Mean lung cancer-related other visit payment (continuous) covariates	Treatment groups (categorical) covariates	Hurdle model: GLM with a gamma distribution and a log link
H ₀ 5m-n: There are no significant differences in the mean lung cancer-related prescription payments by treatment group , for the immunotherapy (m) and targeted therapy (n) groups compared to the chemotherapy group , while controlling for covariates ^a	Mean lung cancer-related prescription payment (continuous) covariates	Treatment groups (categorical) covariates	Hurdle model: GLM with a gamma distribution and a log link
H ₀ 5o-p: There are no significant differences in the mean lung cancer-related total payments by treatment group , for	Mean lung cancer-related total payment (continuous) covariates	Treatment groups (categorical) covariates	Hurdle model: GLM with a gamma distribution and a log link

Objectives/hypotheses	Dependent variables (type)	Independent variables (type)	Statistical analyses
the immunotherapy (o) and targeted therapy (p) groups compared to the chemotherapy group, while controlling for covariates ^a			

^a Covariates include age, gender, race/ethnicity, and urban/rural status.

2.8 Statistical analysis assumptions and sample size calculations

In this section, the statistical analyses are described in more detail. Study assumptions and sample size calculations for each analysis are discussed. All sample size estimations were based on power=0.80, and $\alpha=0.05$. Effect sizes vary depending on the tests being conducted.

2.8.1 Chi-square test

To address objectives 1 and 2, chi-square tests were performed. The assumptions for chi-square tests are: 1) independence of observations; 2) no more than 20% of the expected counts are less than 5; and (3) all individual expected counts are 1 or greater. [143]

For the sample size calculation, a medium effect size ($w=0.3$) based on Cohen's convention, an alpha level of 0.05 and power of 0.80 were used. Using PASS, the required sample size is 108. [144]

2.8.2 ANOVA

To address part of objective 1 (comparison of age across treatment groups), a one-way ANOVA was used. The assumptions for ANOVA are: 1) independence of observations; 2) the

dependent variable is normally distributed in each group; and 3) the variance of data in groups should be equal (homogeneity of variance). [143]

A Q-Q plot was used to test normality. However, ANOVA is a robust test that can tolerate data which is non-normal especially with relatively large sample sizes. [143] Levene's test was used to test the homogeneity of variance. For the sample size calculation, a medium effect size ($w=0.25$) based on Cohen's convention, an alpha level of 0.05 and power of 0.80, and 3 groups were used. Using PASS, the required sample size is 159.

2.8.3 Zero-Inflated Negative Binomial model

A relatively large proportion of subjects may not experience a healthcare event. Zero-inflated regression is a way to model count data with excess zeros. For count data in which the variance exceeds the mean, the negative binomial is more appropriate than the Poisson distribution. [145] Thus, Zero-Inflated Negative Binomial (ZINB) regression was used to address objective 3. Zero-inflated regression can be considered a combination of two statistical processes in which the event count models are not truncated at zero. The subjects with $y = 0$ are considered to consist of two groups: 1) subjects in a perfect state (always zero—it was not possible for subjects to have a value other than zero); and 2) subjects in an imperfect state (y could be > 0 , but they have a value of zero on this measure). The zero-inflated regression generates two separate models and then combines them. First, a logistic regression model is generated for the “certain zero” cases, predicting whether a case falls in this group. Next, a negative binomial model is generated to predict the counts for those cases that are “not certain zeros.” Finally, the two models are combined.

2.8.4 Hurdle (two-step) model

Lung cancer-related payment data were found to be positively skewed and contain zeros. Two-part hurdle models were used for objectives 4 and 5. The analysis takes the form of a logistic regression modeling the probability that the outcome is non-zero, followed by a generalized linear model (GLM) with a gamma distribution and a log link to model the non-zero outcomes which are typically positively skewed.

The assumptions for GLM are: 1) correct specification of the variance function; 2) independence of observations; 3) correct specification of the dispersion effect; 4) correct specification of the link function; 5) correct form for the explanatory variables; and 6) lack of undue influence of individual observations. [143]

The generalized linear model is defined as follows:

$$\text{LogE}(Y|X) = a + b_1X_1 + b_2X_2 + \dots + b_5X_5$$

$E(Y|X)$ = expected predicted value

a = constant

b_n = regression coefficient

X_1 = age

X_2 = gender

X_3 = race/ethnicity

X_4 = region

X_5 = CCI

For the sample size calculation, an alpha level of 0.05 and power of 0.80 were used. Because neither PASS nor G*Power calculates power for GLM analysis, multiple regression was used as a substitute. Since the required sample size of GLM with a gamma distribution will not exceed the sample size of multiple linear regression with a normal distribution with a given

power, the required sample size for GLM would not exceed 403 as calculated by PASS (multiple linear regression with an small effect size of 0.02). [192, 193]

In summary, the minimum required sample size for this study based on the power analyses is 403 (Table 2.8).

Table 2.12 A summary of sample size calculations

	Chi-square test	One-way ANOVA	Multiple linear regression	GLM
Required sample size	108	159	403	<403

Chapter 3 Results

3.1 Chapter overview

This section presents the study results in the order of the objectives.

3.2 Description of case identification

A review of the Texas Medicaid eligibility files identified 26,390 enrollees who were diagnosed with lung cancer in any position during the study period (1/1/2014-6/30/2021). Of these enrollees, 7,357 enrollees (27.9%) were excluded because they did not meet the criterion to be considered newly diagnosed lung cancer patients. Furthermore, 5,815 enrollees (22.0%) having fewer than 2 lung cancer-related medical visits during the post-index period were excluded. To eliminate the influence of cancers other than lung cancer, 2,602 (9.9%) enrollees were excluded because they had other cancer diagnoses during the pre-index period. This study focuses on NSCLC cancer; therefore, 7 (0.03%) patients receiving topotecan or temozolomide for SCLC during the pre-index period were also excluded. Although it is likely that a large majority of the study population were NSCLC patients, we couldn't confirm that the study population consisted only of NSCLC patients since many of the same medicines are prescribed for SCLC and NSCLC patients. Since outpatient prescription medications used by Texas Medicaid enrollees are covered by the Medicare Part D program when enrollees reach 65 years of age and enroll in Medicare, this study only included enrollees aged 18-63 years because prescription medication use would not be captured for those who turned 65 during the 1-year follow-up period. A total of 5,631 enrollees (21.3%) were excluded due to age. Continuous enrollment is required since this study will quantify and compare lung cancer-related healthcare utilization and payments across different treatment groups at the patient level. This criterion further ruled out 3,827 (14.5%) enrollees. After inclusion and exclusion criteria were applied, 1,151 (4.4%) Texas Medicaid enrollees who were 18-63 years old diagnosed with lung cancer

from 7/1/2014 to 6/30/2020 with 2 or more medical visits during the 1-year follow-up period were identified. Of these enrollees, only 453 (1.7%) received National Comprehensive Cancer Network (NCCN) recommended medications for Non-Small Cell Lung Cancer (NSCLC) (see Figure 3.1) and were included in the study analyses.

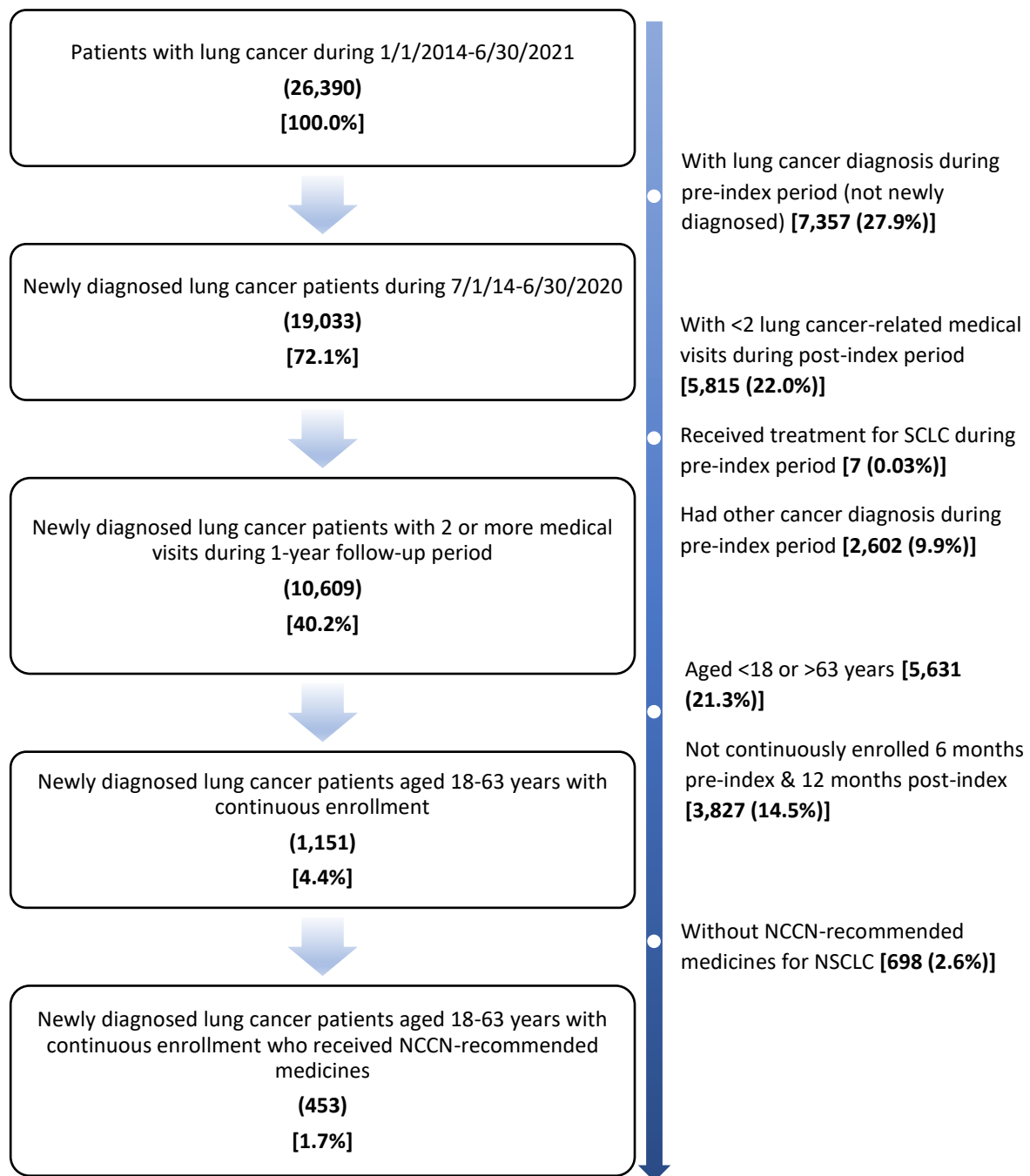


Figure 3.1 Process of case identification

3.3 Objective 1 Demographic characteristics and clinical characteristics

Objective 1 was to describe and compare the demographic characteristics (age, gender, race/ethnicity, and urban/rural status) and CCI scores of the study sample across treatment groups (chemotherapy, targeted therapy, and immunotherapy). Means and standard deviations (SD) were used to describe age, and frequencies and proportions were used to describe all other variables (Table 3.1). The descriptive statistics for the demographic characteristics are based on patient-level data at the index date. The information pertaining to the index-date claim for each patient was used for demographic characteristics, while the information pertaining to the CCI was based on pre-index claims-level data.

Of the 453 lung cancer patients, 364 (80.4%) received chemotherapy, 36 (7.9%) received targeted therapy, and 53 (11.7%) received immunotherapy as the first-line treatment. The mean (SD) age of the overall population was 56.5 (6.0) years, and the mean ages were similar across groups. The mean (SD) ages of the study groups were 56.4 (6.2) years in the chemotherapy group, 56.2 (5.8) years in the targeted therapy group, and 57.5 (5.0) years in the immunotherapy group. An ANOVA test showed no significant difference in the mean ages across treatment groups ($F=0.86$, $p=0.4229$). Thus, “ H_{01a} : There are no significant differences in ages across treatment groups” was not rejected.

The overall sample was predominantly females (258, 57.0%) and that pattern was observed for each treatment group [203 (55.8%) for the chemotherapy group, 20 (55.6%) for the targeted therapy group, and 35 (66.0%) for the immunotherapy group]. A chi-square test indicated that there was no significant difference in gender across treatment groups (Pearson chi-square=2.0209, $p=0.3641$). Thus, “ H_{01b} : There are no significant differences in gender across treatment groups” was not rejected.

Regarding race/ethnicity of the study sample, Whites accounted for the largest proportion (41.5%) of the study sample, followed by Blacks (24.9%). “Others” including American Indians, Asians and unknown accounted for 19.9% and Hispanics accounted for 13.7%. Similar patterns were seen in the chemotherapy and immunotherapy groups. In the targeted therapy group, Whites were still the major group (38.9%), followed by Hispanics (25.0%), Blacks (22.2%) and others (13.9%). A chi-square test showed no significant differences in race/ethnicity across treatment groups (Pearson chi-square=9.1014, $p=0.1680$). Thus, “H₀1c: There are no significant differences in race/ethnicity across treatment groups” was not rejected.

Lung cancer patients in this study were mainly from urban areas (308, 68.6%) in Texas with 141 (31.4%) from rural areas. Enrollees from urban areas accounted for 68.6% of patients in the chemotherapy group, 69.4% in the targeted therapy group, and 67.9% in the immunotherapy group. A small number of enrollees (4, <0.01%) had missing information about urban/rural status. A chi-square test showed no significant difference in urban/rural status across treatment groups (Pearson chi-square=0.0232, $p=0.9885$). Thus, “H₀1d: There are no significant differences in urban/rural status across treatment groups” was not rejected.

Lung cancer diagnoses were excluded when calculating CCI scores. A plurality of the study sample (183, 40.4%) had a CCI score of 1. About one-fourth of enrollees had a CCI score of 0 (102, 22.5%), and a similar number of enrollees (100, 22.1%) had a CCI score of 2. A relatively small number of enrollees (68, 15.0%) had a CCI score ≥ 3 . Similar patterns were found across treatment groups. A chi-square test showed no significant difference in CCI scores across treatment groups (Pearson chi-square=3.3537, $p=0.7765$) and thus, “H₀1e: There are no significant differences in CCI values across treatment groups” was not rejected.

Table 3.1 Demographic characteristics of the study sample

Characteristics	All N=453 100.0%	Chemotherapy N=364 (80.4%)	Targeted therapy N=36 (7.9%)	Immunotherapy N=53 (11.7%)	P value ^a
Age					
Mean (SD)	56.5 (6.0)	56.4 (6.2)	56.2 (5.8)	57.5 (5.0)	0.4229
Sex [N (%)]					
Female	258 (57.0)	203 (55.8)	20 (55.6)	35 (66.0)	0.3641
Male	195 (43.0)	161 (44.3)	16 (44.4)	18 (34.0)	
Race/ethnicity [N (%)]					
White	188 (41.5)	158 (43.4)	14 (38.9)	16 (30.2)	0.1680
Black	113 (24.9)	89 (24.5)	8 (22.2)	16 (30.2)	
Hispanic	62 (13.7)	47 (12.9)	9 (25.0)	6 (11.3)	
Others	90 (19.9)	70 (19.2)	5 (13.9)	15 (28.3)	
Region [N (%)]					
Rural	141 (31.4)	113 (31.4)	11 (30.6)	17 (32.1)	0.9885
Urban	308 (68.6)	247 (68.6)	25 (69.4)	36 (67.9)	
Unknown	4 (<0.01)				
CCI [N (%)]					
0	102 (22.5)	80 (22.0)	9 (25.0)	13 (24.5)	0.7765
1	183 (40.4)	153 (42.0)	11 (30.6)	19 (35.9)	
2	100 (22.1)	80 (22.0)	8 (22.2)	12 (22.6)	
≥3	68 (15.0)	51 (14.0)	8 (22.2)	9 (17.0)	

a: An ANOVA was used to compare mean ages across groups and chi-square analyses were used to compare all other variables.

3.4 Objective 2 Treatment patterns

Objective 2 was to describe and compare treatment patterns in terms of treatment groups and treatment regimens by treatment line.

3.4.1 Treatment groups by treatment line

The numbers and proportions of patients receiving chemotherapy, targeted therapy, and immunotherapy by treatment line are presented in Table 3.2. Chemotherapy was the most frequently prescribed first-line treatment for enrollees with lung cancer (363, 80.1%). Immunotherapy (53, 11.7%) exceeded targeted therapy (37, 8.2%), becoming the second most commonly used first-line treatment. About one-third of enrollees (146) received second-line treatment. Only 31 enrollees received third-line and 7 enrollees received fourth-line treatment. Treatments enrollees received after first line are collectively referred to as subsequent line-treatment in this study. In subsequent-line therapy, 85 (46.2%) enrollees received chemotherapy, 79 (42.9%) enrollees received immunotherapy, and 20 (10.9%) enrollees received targeted therapy. A Pearson chi-square test showed that there were significant differences in proportions of patients receiving chemotherapy, targeted therapy, and immunotherapy by treatment line (chi-square=84.1017, $p<0.0001$). Thus, “ H_0 2a: There are no significant differences in proportions of patients in treatment groups by treatment line” was rejected.

Table 3.2 Total numbers and proportions of patients receiving chemotherapy, targeted therapy, and immunotherapy by treatment line

Treatment line	Chemotherapy	Targeted therapy	Immunotherapy	Chi-square P value
First line [N (%)]	363 (80.1)	37 (8.2)	53 (11.7)	84.1017 <0.0001
Subsequent line [N (%)]	85 (46.2)	20 (10.9)	79 (42.9)	

Note: Subsequent line includes second-line treatment (146 enrollees), third-line treatment (31 enrollees), and fourth-line treatment (7 enrollees).

3.4.2 Treatment regimens by treatment line

Table 3.3 shows treatment regimens in first and subsequent lines. In general, platinum-based treatments accounted for the majority of first-line treatments (platinum-taxane doublet regimen: 30.9%; platinum-nontaxane doublet regimen: 35.3%), while singlet immunotherapy was the most commonly used treatment in subsequent-line treatment (35.9%). Triplet therapy with cisplatin or carboplatin and doublet regimens without platinum were prescribed least in both first- and subsequent-line treatments. A chi-square test showed a significant difference in proportions of patients receiving different treatments by treatment line (chi-square=185.6896, $p<0.0001$). Thus, “H₀2b: There are no significant differences in proportions of patients receiving different treatment regimens by treatment line” was rejected.

3.4.3 Chemotherapy regimens by treatment line

All chemotherapy treatments were more common in first line compared to subsequent line except for single-agent chemotherapy other than carboplatin and cisplatin. In first-line treatment, carboplatin or cisplatin plus a nontaxane regimen (vinorelbine, etoposide, pemetrexed, or gemcitabine) was the most frequently prescribed treatment (160; 44.1%). Carboplatin or cisplatin plus a taxane regimen (paclitaxel or docetaxel) was also prescribed widely (140; 38.6%). The number of patients receiving carboplatin/cisplatin (30; 8.3%) and single-agent chemotherapy other than carboplatin/cisplatin (25; 6.9%) were similar. Only a small number of patients received doublet regimens without platinum. Triplet therapy with cisplatin or carboplatin was prescribed least in first line. The treatment pattern in subsequent line differed from that in first line. Single-agent therapy without cisplatin or carboplatin accounted for the largest proportion (39; 45.9%), followed by the platinum-taxane doublet regimen (23; 27.1%), and the platinum-nontaxane doublet regimen (14; 16.5%). A Fisher’s exact test was used instead of Pearson chi-square since the cell size assumption was violated. The Fisher’s exact test showed

a significant difference in proportions of patients receiving different chemotherapy treatment regimens by treatment line ($p < 0.0001$). Thus, “H₀2c: There are no significant differences in proportions of patients receiving chemotherapy regimens by treatment line” was rejected.

3.4.4 Targeted therapy regimens by treatment line

A small proportion of patients received targeted therapy. Single targeted therapy was used more often compared to doublet and triplet targeted therapy in both first and subsequent lines (first line: 21 (56.8%) vs. 16 (43.2%)). A chi-square test showed no significant differences in proportions of patients receiving different targeted treatment regimens by treatment line (chi-square=0.0163, $p = 0.8985$). Thus, “H₀2d: There are no significant differences in proportions of patients receiving targeted therapy regimens by treatment line” was not rejected.

3.4.5 Immunotherapy regimens by treatment line

As for immunotherapy, doublet/triplet immunotherapy was more common in first line (33 (62.3%) vs. 20 (37.7%)), while singlet immunotherapy was prescribed more often in subsequent line (66 (83.5%) vs. 13 (16.5%)). A chi-square test showed a significant difference in proportions of patients receiving different immunotherapy regimens by treatment line (chi-square=29.3165, $p < 0.0001$). Thus, “H₀2e: There are no significant differences in proportions of patients receiving immunotherapy regimens by treatment line” was rejected.

Table 3.3 Total numbers and proportions of patients receiving treatments by treatment group and treatment line

Treatment group	Treatment regimen	First line N (group col%) [overall col%]	Subsequent line N (group col%) [overall col%]	Chi-square P value	
				Group	Overall
Chemotherapy	Platinum-taxane doublet regimen	140 (38.6) [30.9]	23 (27.1) [12.5]	89.8920 <0.0001	185.6896 <0.0001
	Platinum-nontaxane doublet regimen	160 (44.1) [35.3]	14 (16.5) [7.6]		
	Doublet regimens without platinum	*	*		
	Triplet therapy with platinum	*	*		
	Cisplatin or carboplatin alone	30 (8.3) [6.6]	*		
	Other single-agent chemotherapy	25 (6.9) [5.5]	39 (45.9) [21.2]		
Targeted therapy	Single targeted therapy	21 (56.8) [4.6]	*	0.0163 0.8985	
	Doublet/triplet targeted therapy	16 (43.2) [3.5]	*		
Immunotherapy	Singlet immunotherapy	20 (37.7) [4.4]	66 (83.5) [35.9]	29.3165 <0.0001	
	Doublet/triplet immunotherapy	33 (62.3) [7.3]	13 (16.5) [7.1]		

*Cells with <11 patients were not reported according to Texas Medicaid requirements

3.4.6 Top 5 Treatments by treatment line

To further explore treatment patterns in first and subsequent treatment lines, the top 5 treatments prescribed in each treatment group are detailed in Table 3.4. In first-line treatment, chemotherapy was the most commonly used treatment group and carboplatin-based chemotherapy accounted for the largest proportion. Carboplatin-paclitaxel was the most frequently prescribed treatment regimen (123; 33.9%), followed by carboplatin-etoposide (52; 14.3%), cisplatin-etoposide (50; 13.8%), carboplatin-pemetrexed (35; 9.6%), and carboplatin/cisplatin (20; 5.5%). The immunotherapy group accounted for the second largest proportion of lung cancer-related treatments. About half of immunotherapy regimens were triplet immunotherapy with pembrolizumab. The targeted therapy group was prescribed least in first-line treatment. Bevacizumab was the most frequently used targeted regimen.

In subsequent-line treatment, the immunotherapy group, especially singlet immunotherapy regimens, and chemotherapy were used more frequently compared to targeted therapy. With respect to immunotherapy, nivolumab was predominately prescribed (30; 38.0%), followed by durvalumab (16; 20.2%), and pembrolizumab (15; 19.0%). Pemetrexed-pembrolizumab, carboplatin-paclitaxel-pembrolizumab, and carboplatin-etoposide-atezolizumab accounted for small proportions of lung cancer-related immunotherapy. As for chemotherapy in subsequent line, carboplatin-paclitaxel was still the most frequently used treatment (20; 23.5%). More singlet chemotherapy regimens were used in subsequent line compared to that in first line (paclitaxel: 15 (17.6%); pemetrexed: 12 (14.1%)). Similar to the treatment pattern in first line, the targeted therapy group was still prescribed least in subsequent line with bevacizumab as the most frequently used targeted regimen.

Table 3.4 Top 5 treatments prescribed by treatment group and treatment line

Treatment regimens		Number	Treatment group col% ¹	Overall col% ¹
First-line treatment				
Chemotherapy	Carboplatin-paclitaxel	123	33.9	27.2
	Carboplatin-etoposide	52	14.3	11.5
	Cisplatin-etoposide	50	13.8	11.0
	Carboplatin-pemetrexed	35	9.6	7.7
	Carboplatin/cisplatin	20	5.5	4.4
Targeted therapy	Bevacizumab	12	32.4	2.6
	Carboplatin-paclitaxel-bevacizumab	*	*	*
	Carboplatin-pemetrexed-bevacizumab	*	*	*
	Osimertinib	*	*	*
	Dacomitinib	*	*	*
Immunotherapy	Carboplatin-pemetrexed-pembrolizumab	20	37.3	4.4
	Pembrolizumab	13	24.5	2.9
	Carboplatin-etoposide-atezolizumab	*	*	*
	Carboplatin-paclitaxel-pembrolizumab	*	*	*
	Nivolumab	*	*	*
Subsequent-line treatment				
Chemotherapy	Carboplatin-paclitaxel	20	23.5	10.9
	Paclitaxel	15	17.6	8.2
	Pemetrexed	12	14.1	6.5
	Carboplatin/Cisplatin	*	*	*
	Carboplatin-pemetrexed	*	*	*
	Carboplatin-gemcitabine	*	*	*
	Docetaxel	*	*	*
	Gemcitabine	*	*	*
Targeted therapy	Bevacizumab	*	*	*
	Osimertinib	*	*	*
	Bevacizumab-pemetrexed	*	*	*
	Carboplatin-bevacizumab-pemetrexed	*	*	*
	Bevacizumab-paclitaxel	*	*	*
Immunotherapy	Nivolumab	30	38.0	16.3
	Durvalumab	16	20.2	8.7
	Pembrolizumab	15	19.0	8.2
	Pemetrexed-pembrolizumab	*	*	*
	Carboplatin-paclitaxel-pembrolizumab	*	*	*

	Treatment regimens	Number	Treatment group col% ¹	Overall col% ¹
	Carboplatin-etoposide-atezolizumab	*	*	*

1. Only the top 5 treatment regimens in each treatment group are reported; the percentages are based on all regimens in each treatment group. Treatment group col% = N of treatment regimens/N of treatment regimens within each treatment group by treatment line; Overall col% = N of treatment regimens/N of treatment regimens by treatment line

*Cells with <11 patients were not reported according to Texas Medicaid requirements

3.5 Objective 3 Healthcare utilization

Objective 3 was to compare lung cancer-related healthcare utilization among lung cancer patients in terms of hospitalizations, inpatient hospital days, ED visits, office visits, hospital outpatient visits, home visits, and other visits by treatment group. Figures 3.2a and 3.2b display healthcare utilization for the overall population and for patients who had healthcare visits. A brief summary of descriptive analysis results is presented in each section.

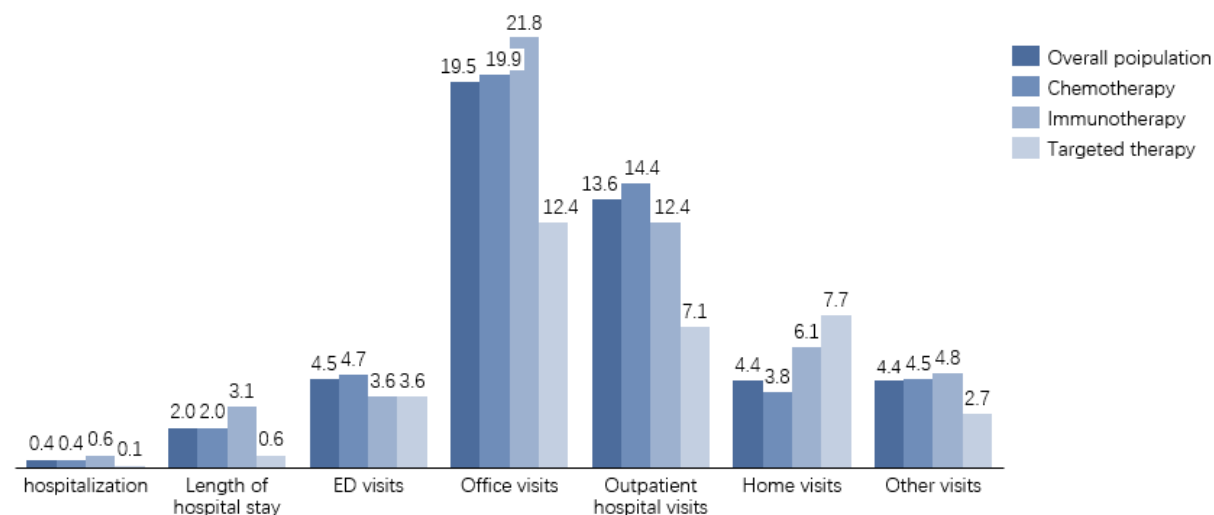


Figure 3.2a Average number of healthcare utilization events per patient during 1-year follow-up period for entire population

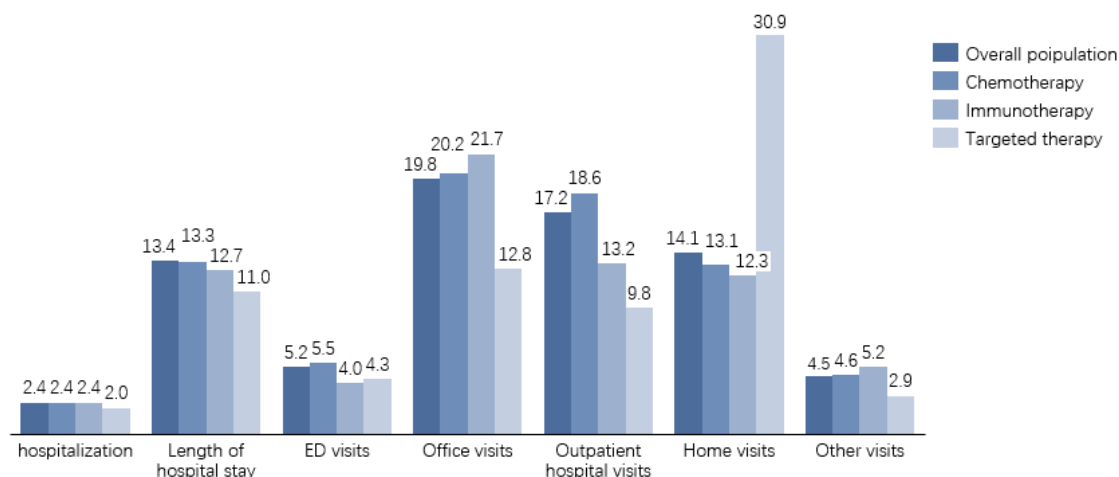


Figure 3.2b Average number of healthcare utilization events per patient during 1-year follow-up period for patients experiencing healthcare visits

3.5.1 Hospitalizations

The average number of hospitalizations for all patients was 0.36 (SD: 1.36) during 1-year follow-up period. The average number of hospitalizations for patients receiving chemotherapy (mean: 0.36; SD: 1.37) was similar to the overall population. Patients with immunotherapy (mean: 0.58; SD: 1.66) had more hospitalizations compared to the overall population, while patients with targeted therapy (mean: 0.11; SD: 0.46) had fewer hospitalizations compared to the overall population. However, only 70 (15.5%) patients had hospitalizations. For patients with hospitalization, the mean (SD) number of hospitalizations was 2.4 (2.7), with 2.4 (2.8) for the chemotherapy group, 2.4 (2.7) for the immunotherapy group, and 2.0 (2.0) for the targeted therapy group. Note that the zero-inflated negative binomial model did not converge; therefore, no inferential comparison was conducted. The descriptive results should be interpreted with caution.

3.5.2 Length of hospital stay

The average length of hospital stay for the overall population during 1-year follow-up period was 2.0 days, which is smaller than the standard deviation (6.6). The average length of hospital stay for patients receiving chemotherapy (mean: 2.0; SD: 6.9) was similar to the overall population. Patients with immunotherapy (mean: 3.1; SD: 6.8) had more days of hospital stay compared to the overall population, while patients with targeted therapy (mean: 0.6; SD: 2.6) had much fewer days of hospital stay compared to the overall population. Among patients having hospitalization (70, 15.5%), the average (SD) length of hospital stay was 13.4 (12.6) days, with 13.3 (10.0) days for the chemotherapy group, 12.7 (8.4) days for the immunotherapy group, and 11.0 (2.8) days for the targeted therapy group.

The results for inpatient length of hospital stay are shown in Table 3.6. The expected number of inpatient hospital days for the immunotherapy group is 1.0672 times ($e^{0.0650}$) the expected number of inpatient hospital days for the chemotherapy group while holding all other variables in the model constant (Wald Chi-square=0.10, p=0.7508). The expected number of inpatient hospital days for the targeted therapy group is 0.9735 times ($e^{-0.0269}$) the expected number of inpatient hospital days for the chemotherapy group while holding all other variables in the model constant (Wald Chi-square=0.00, p=0.9567). These relationships were not significant; thus, “H₀3c-d: There are no significant relationships in the number of lung cancer-related inpatient hospital days for the immunotherapy (c) and targeted therapy (d) groups compared to the chemotherapy group, while controlling for covariates” were not rejected.

Table 3.6 Comparison of differences in length of hospital stay by treatment group, while controlling for covariates*

Variables	Exponentiated Estimate (IRR)	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi- Square	P value
Treatment group (ref=Chemotherapy)							
Immunotherapy	1.0672	0.0650	0.2045	-0.3359	0.4658	0.10	0.7508
Targeted therapy	0.9735	-0.0269	0.4958	-0.9986	0.9448	0.00	0.9567
Age							
18-63 years old	1.0248	0.0245	0.0196	-0.014	0.063	1.55	0.2128
Gender (ref=Female)							
Male	1.0802	0.0771	0.1653	-0.274	0.4012	0.22	0.641
Race (ref=White)							
Black	0.9399	-0.062	0.2573	-0.5662	0.4422	0.06	0.8096
Hispanic	1.0765	0.0737	0.2839	-0.4828	0.6302	0.07	0.7952
Others	1.3040	0.2654	0.2034	-0.1333	0.664	1.7	0.1920
Area (ref=Urban)							
Rural	0.8193	-0.1993	0.1632	-0.5192	0.1206	1.49	0.2221
CCI (ref=0)							
1	1.0317	0.0312	0.2551	-0.4687	0.5311	0.01	0.9027
2	1.0498	0.0486	0.2939	-0.5275	0.6246	0.03	0.8688
≥3	1.1005	0.0958	0.2807	-0.4543	0.6458	0.12	0.7330
Intercept	2.6896	0.9894	1.1385	-1.242	3.2208	0.76	0.3848

* Zero-inflated negative binomial regression was used for this analysis.

IRR = Incident Rate Ratio

3.5.3 ED visits

Of the 453 lung cancer patients, 390 (86.1%) had ED visits during 1-year follow-up period. The mean (SD) of ED visits for all patients was 4.5 (6.2). The average number of ED visits for patients receiving chemotherapy (mean: 4.7; SD: 6.7) was similar to the overall population. Patients with immunotherapy (mean: 3.6; SD: 3.8) and targeted therapy (mean: 3.6; SD: 3.1) had fewer ED visits compared to the overall population. For patients having ED visits, the mean (SD)

of ED visits was 5.2 (6.4), with 5.5 (6.9) for the chemotherapy group, 4.0 (3.8) for the immunotherapy group and 4.3 (2.9) for the targeted therapy group.

Table 3.7 shows the results of the zero-inflated negative binomial regression analysis for ED visits. The expected number of ED visits for the immunotherapy group is 0.7336 times ($e^{-0.3098}$) the expected number of ED visits for the chemotherapy group while holding all other variables in the model constant (Wald Chi-square=4.01, $p=0.0452$). The expected number of ED visits for the targeted therapy group is 0.8708 times ($e^{-0.1383}$) the expected number of ED visits for the chemotherapy group while holding all other variables in the model constant (Wald Chi-square=0.54, $p=0.4615$). Thus, “H₀3e-f: There are no significant relationships in the number of lung cancer-related ED visits for the immunotherapy (e) and targeted therapy (f) groups compared to the chemotherapy group, while controlling for covariates” was rejected for H₀3e (immunotherapy group) but not rejected for H₀3f (targeted therapy group).

Table 3.7 Comparison of differences in ED visits by treatment group, while controlling for covariates*

Variables	Exponentiated Estimate (IRR)	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	P value
Treatment group (ref=Chemotherapy)							
Immunotherapy	0.7336	-0.3098	0.1547	-0.6131	-0.0066	4.01	0.0452
Targeted therapy	0.8708	-0.1383	0.1877	-0.5062	0.2297	0.54	0.4615
Age							
18-63 years old	0.9834	-0.0167	0.008	-0.0324	-0.001	4.36	0.0368
Gender (ref=Female)							
Male	0.8381	-0.1766	0.0988	-0.3703	0.017	3.2	0.0738
Race (ref= White)							
Black	1.2566	0.2284	0.1238	-0.0142	0.471	3.4	0.065
Hispanic	1.1348	0.1265	0.1605	-0.188	0.441	0.62	0.4305
Others	1.5333	0.4274	0.1323	0.1681	0.6867	10.44	0.0012
Area (ref=Urban)							
Rural	0.8755	-0.133	0.1074	-0.3436	0.0775	1.53	0.2155
CCI (ref=0)							
1	1.2312	0.208	0.1337	-0.0541	0.47	2.42	0.1198
2	1.5496	0.438	0.1486	0.1468	0.7929	8.69	0.0032
≥3	1.7642	0.5677	0.1627	0.2489	0.8865	12.18	0.0005
Intercept	8.5986	2.1516	0.4603	1.2495	3.0538	21.85	<0.0001

* Zero-inflated negative binomial regression was used for this analysis.

IRR = Incident Rate Ratio

3.5.4 Office visits

Of the 453 lung cancer patients, 350 (77.3%) had office visits during 1-year follow-up period. The mean (SD) number of office visits for overall population was 19.5 (23.1). The average number of office visits for patients receiving chemotherapy (mean: 19.9; SD: 24.1) was similar to the overall population. Patients with immunotherapy (mean: 21.8; SD: 18.4) had more office visits compared to the overall population, while patients with targeted therapy (mean: 12.4; SD: 18.1) had fewer office visits compared to overall population. For those having office visits, the mean

(SD) number of office visits was 19.8 (23.3), with 20.2 (24.2) for the chemotherapy group, 21.7 (18.5) for the immunotherapy group, and 12.8 (19.2) for the targeted therapy group.

Table 3.8 shows the results of the zero-inflated negative binomial regression analysis for office visits. The expected number of office visits for the immunotherapy group is 1.0112 times ($e^{-0.0111}$) the expected number of office visits for the chemotherapy group while holding all other variables in the model constant (Wald Chi-square=0.00, $p=0.957$). The expected number of office visits for the targeted therapy group is 0.7898 times ($e^{-0.236}$) the expected number of office visits for the chemotherapy group while holding all other variables in the model constant (Wald Chi-square=0.6900, $p=0.4036$). Thus, “ H_0 3g-h: There are no significant relationships in the number of lung cancer-related office visits for the immunotherapy (g) and targeted therapy (h) groups compared to the chemotherapy group, while controlling for covariates” were not rejected.

Table 3.8 Comparison of differences in office visits by treatment group, while controlling for covariates*

Variables	Exponentiated Estimate (IRR)	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi- Square	P value
Treatment group (ref=Chemotherapy)							
Immunotherapy	1.0112	0.0111	0.2049	-0.3906	0.4127	0.00	0.957
Targeted therapy	0.7898	-0.236	0.2841	-0.7929	0.3209	0.6900	0.4063
Age							
18-63 years old	1.0142	0.0141	0.0141	-0.0135	0.0417	1	0.3171
Gender (ref=Female)							
Male	1.0298	0.0294	0.1402	-0.2454	0.3042	0.04	0.8337
Race (ref=White)							
Black	0.7552	-0.2808	0.1741	-0.6221	0.0605	2.6	0.1068
Hispanic	0.7151	-0.3353	0.2239	-0.7742	0.1036	2.24	0.1343
Others	0.8128	-0.2073	0.1862	-0.5723	0.1576	1.24	0.2654
Area (ref=Urban)							
Rural	1.0291	0.0287	0.152	-0.2691	0.3266	0.04	0.85
CCI (ref=0)							
1	0.9923	-0.0077	0.1982	-0.3962	0.3808	0	0.969
2	0.8587	-0.1523	0.2159	-0.5755	0.271	0.5	0.4808
≥3	1.1187	0.1122	0.239	-0.3562	0.5806	0.22	0.6387
Intercept	11.5018	2.4425	0.8352	0.8055	4.0794	8.55	0.0035

* Zero-inflated negative binomial regression was used for this analysis.

IRR = Incident Rate Ratio

3.5.5 Hospital outpatient visits

Of the 453 lung cancer patients, 358 (79.0%) had hospital outpatient visits during 1-year follow-up period. The mean (SD) number of hospital outpatient visits for the overall population was 13.6 (19.2). The average number of hospital outpatient visits for patients receiving chemotherapy (mean: 14.4; SD: 20.1) was similar to the overall population. The average number of hospital outpatient visits for patients with immunotherapy (mean: 12.4; SD: 16.2) was lower than the overall population and patients in targeted therapy (mean: 7.1; SD: 12.6) had much fewer

office visits compared to the overall population. For those having hospital outpatient visits, the mean (SD) number was 17.2 (20.1), with 18.6 (21.0) for the chemotherapy group, 13.2 (16.4) for the immunotherapy group, and 9.8 (14.0) for the targeted therapy group.

Table 3.9 shows the results of the ZINB regression analysis for hospital outpatient visits. The expected number of hospital outpatient visits for the immunotherapy group is 0.69 times ($e^{-0.3702}$) the expected number of hospital outpatient visits for the chemotherapy group while holding all other variables in the model constant (Wald Chi-square=3.37, $p=0.0665$). The expected number of hospital outpatient visits for the targeted therapy group is 0.45 times ($e^{-0.8071}$) the expected number of hospital outpatient visits for the chemotherapy group while holding all other variables in the model constant (Wald Chi-square=10.81, $p=0.001$). Thus, “ H_{03i-j} : There are no significant relationships in the number of lung cancer-related hospital outpatient visits for the immunotherapy (i) and targeted therapy (j) groups compared to the chemotherapy group, while controlling for covariates” was not rejected for H_{03i} (immunotherapy group) but was rejected for H_{03j} (targeted therapy group).

Table 3.9 Comparison of differences in hospital outpatient visits by treatment group, while controlling for covariates

Variables	Exponentiated Estimate (IRR)	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi- Square	P value
Treatment group (ref=Chemotherapy)							
Immunotherapy	0.6906	-0.3702	0.2017	-0.7655	0.0252	3.37	0.0665
Targeted therapy	0.4462	-0.8071	0.2455	-1.2882	-0.326	10.81	0.001
Age							
18-63 years old	0.9806	-0.0196	0.0126	-0.0444	0.0051	2.42	0.1199
Gender (ref=Female)							
Male	0.9271	-0.0757	0.1432	-0.3564	0.2049	0.28	0.5969
Race (ref=White)							
Black	1.4865	0.3964	0.1695	0.0643	0.7285	5.47	0.0193
Hispanic	0.7426	-0.2976	0.2345	-0.7571	0.1619	1.61	0.2043
Others	1.5290	0.4246	0.1824	0.067	0.7822	5.42	0.0199
Area (ref=Urban)							
Rural	0.9081	-0.0964	0.1455	-0.3815	0.1887	0.44	0.5076
CCI (ref=0)							
1	1.4205	0.351	0.1867	-0.0149	0.717	3.53	0.0601
2	1.4351	0.3612	0.2127	-0.0557	0.778	2.88	0.0895
≥3	1.3254	0.2817	0.2279	-0.1649	0.7283	1.53	0.2164
Intercept	34.1137	3.5297	0.7064	2.1452	4.9142	24.97	<0.0001

* Zero-inflated negative binomial regression was used for this analysis.

IRR = Incident Rate Ratio

3.5.6 Home visits

Of the 453 lung cancer patients, only 140 (30.9%) had home visits during 1-year follow-up period. The mean (SD) number of home visits for the overall population was 4.4 (16.1). The average number of home visits for patients receiving chemotherapy (mean: 3.8; SD: 15.3) was slightly lower than the overall population. The average numbers of home visits for patients with immunotherapy (mean: 6.1; SD: 11.2) and targeted therapy (mean: 7.7; SD: 26.5) were higher than the overall population. For those having home visits, the mean (SD) number was 14.1 (26.5), with

13.1 (26.4) for the chemotherapy group, 12.3 (13.4) for the immunotherapy group, and 30.9 (47.6) for the targeted therapy group. However, the zero-inflated negative binomial model did not converge given the limited sample size; therefore, no inferential comparison was conducted. The descriptive results should be interpreted with caution.

3.5.7 Other visits

Of the 453 lung cancer patients, 253 (55.8%) had other visits during 1-year follow-up period. The mean (SD) number of other visits for overall population was 4.4 (8.1). The average numbers of other visits for patients receiving chemotherapy (mean: 4.5; SD: 8.6) and immunotherapy (mean: 4.8; SD: 5.0) were similar to the overall population, while the average number of other home visits for patients receiving targeted therapy (mean: 2.7; SD: 4.8) was much lower than the overall population. For those having other visits, the mean (SD) number was 4.5 (8.2), with 4.6 (8.8) for the chemotherapy group, 5.2 (5.2) for the immunotherapy group, and 2.9 (5.0) for the targeted therapy group.

Table 3.10 shows the results of the zero-inflated negative binomial regression analysis for other visits. The expected number of other visits for the immunotherapy group is 0.7442 times ($e^{-0.2955}$) the expected number of other visits for the chemotherapy group while holding all other variables in the model constant (Wald Chi-square=1.33, p=0.248). The expected number of other visits for the targeted therapy group is 0.8416 times ($e^{-0.1724}$) the expected number of other visits for the chemotherapy group while holding all other variables in the model constant (Wald Chi-square=0.2, p=0.6541). Thus, “H₀3m-n: There are no significant relationships in the number of other lung cancer-related visits by treatment group, for the immunotherapy (m) and targeted

therapy (n) groups compared to the chemotherapy group, while controlling for covariates” were not rejected.

Table 3.10 Comparison of differences in other visits by treatment group, while controlling for covariates*

Variables	Exponentiated Estimate (IRR)	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	P value
Treatment group (ref=Chemotherapy)							
Immunotherapy	0.7442	-0.2955	0.2558	-0.7968	0.2059	1.33	0.248
Targeted therapy	0.8416	-0.1724	0.3847	-0.9265	0.5817	0.2	0.6541
Age							
18-63 years old	0.9674	-0.0331	0.0171	-0.0667	0.0005	3.74	0.0533
Gender (ref=Female)							
Male	0.8423	-0.1716	0.1805	-0.5255	0.1822	0.9	0.3417
Race (ref=White)							
Black	1.1376	0.1289	0.2395	-0.3404	0.5983	0.29	0.5903
Hispanic	0.7412	-0.2995	0.314	-0.9149	0.3158	0.91	0.3401
Others	1.0610	0.0592	0.2463	-0.4236	0.5419	0.06	0.8101
Area (ref=Urban)							
Rural	0.9549	-0.0462	0.2073	-0.4525	0.36	0.05	0.8235
CCI (ref=0)							
1	1.2019	0.1839	0.2581	-0.322	0.6898	0.51	0.4761
2	0.9365	-0.0656	0.3165	-0.686	0.5547	0.04	0.8358
≥3	1.2780	0.2453	0.3159	-0.3739	0.8645	0.6	0.4375
Intercept	39.4053	3.6739	1.0084	1.6975	5.6502	13.27	0.0003

* Zero-inflated negative binomial regression was used for this analysis.

IRR = Incident Rate Ratio

3.6 Objective 4 Healthcare payment status

Six patients were excluded from cost analyses since no visits of any type occurred. Objective 4 was to compare lung cancer-related payment status among patients in terms of payments for hospitalizations, ED visits, office visits, hospital outpatient visits, home visits, other visits, prescriptions, and total payments between immunotherapy group or targeted therapy group

and chemotherapy group, while controlling for covariates. Payment status was a dichotomized variable where 0 = no payments and 1 = payments >\$0.

3.6.1 Hospitalization payment status

Logistic regression results evaluating hospitalization payment status are shown in Table 3.11. Compared to the chemotherapy group, the immunotherapy group was 74.0% more likely to have a hospitalization payment (OR=1.740; 95% CI: 0.855 to 3.541; Wald Chi-square=2.3347; p=0.1265), while the targeted therapy group was 66.0% less likely to have a hospitalization payment (OR=0.340; 95% CI: 0.078 to 1.481; Wald Chi-square=2.0658; p=0.1506), while controlling for other covariates. However, these relationships were not significant. Thus, “H₀4a-b: There are no significant relationships in lung cancer-related hospitalization payment status by treatment group, for the immunotherapy (a) and targeted therapy (b) groups compared to the chemotherapy group, while controlling for covariates” were not rejected.

With every one-year increase in age, the OR of having a hospitalization payment increased 5.4% (OR=1.054; 95% CI: 0.996 to 1.116; Wald Chi-square=3.2980; p=0.0694). Compared to females, males were 29.1% less likely to have a hospitalization payment (OR=0.709; 95% CI: 0.410 to 1.227; Wald Chi-square=1.5128; p=0.2187). Compared to Whites, African Americans were 36.9% less likely to have a hospitalization payment (OR=0.631; 95% CI: 0.306 to 1.300; Wald Chi-square=1.5588; p=0.2118); Hispanics were 14.2% less likely to have a hospitalization payment (OR=0.858; 95% CI: 0.355 to 2.074; Wald Chi-square=0.1159; p=0.7335); and others were 25.0% more likely to have a hospitalization payment (OR=1.250; 95% CI: 0.632-2.474; Wald Chi-square=0.4120; p=0.5210). Compared to patients living in urban areas, patients living in rural areas were 44.2% more likely to have a hospitalization payment (OR=1.442; 95% CI: 0.828 to

2.513; Wald Chi-square=1.6735; p=0.1958). Compared to patients without comorbidities (CCI=0), patients with CCI=1 were 31.3% more likely to have a hospitalization payment (OR=1.313; 95% CI: 0.590 to 2.922; Wald Chi-square=0.4455; p=0.5045), while patients with CCI=2 were 94.8% more likely to have a hospitalization payment (OR=1.948; 95% CI: 0.840 to 4.520; Wald Chi-square=2.4118; p=0.1204), and patients with $CCI \geq 3$ were 86.4% more likely to have a hospitalization payment (OR=1.864; 95% CI: 0.747 to 4.654; Wald Chi-square=1.7815; p=0.1820). All results were while controlling for covariates.

Table 3.11 Logistic regression evaluating hospitalization payment status (dichotomous)*

Variables	Estimate	Wald Chi-Square	P value	OR	Wald 95% Confidence Limits	
Treatment group (ref=Chemotherapy)						
Immunotherapy	0.5539	2.3347	0.1265	1.740	0.855	3.541
Targeted therapy	-1.0798	2.0658	0.1506	0.340	0.078	1.481
Age						
18-63 years old	0.0528	3.2980	0.0694	1.054	0.996	1.116
Gender (ref=Female)						
Male	-0.3442	1.5128	0.2187	0.709	0.410	1.227
Race (ref=White)						
African American	-0.4603	1.5588	0.2118	0.631	0.306	1.300
Hispanic	-0.1533	0.1159	0.7335	0.858	0.355	2.074
Others	0.2234	0.4120	0.5210	1.250	0.632	2.474
Area (ref=Urban)						
Rural	0.3663	1.6735	0.1958	1.442	0.828	2.513
CCI (ref=0)						
1	0.2724	0.4455	0.5045	1.313	0.590	2.922
2	0.6668	2.4118	0.1204	1.948	0.840	4.520
≥3	0.6230	1.7815	0.1820	1.864	0.747	4.654
Intercept	-5.0203	8.7769	0.0031	0.0066		

* 0=no payments and 1=payments >\$0

3.6.2 ED visit payment status

Logistic regression results evaluating ED visit payment status are shown in Table 3.12. Compared to the chemotherapy group, the immunotherapy group was 10.4% more likely to have ED visit payments (OR=1.104; 95% CI: 0.557 to 2.189; Wald Chi-square=0.0806; p=0.7765); and the targeted therapy group was 13.4% less likely to have ED visit payments (OR=0.866; 95% CI: 0.393 to 1.907; Wald Chi-square=0.1277; p=0.7208), while controlling for other covariates. However, these relationships were not significant. Thus, “H₀4c-d: There are no significant relationships in lung cancer-related ED visit payment status by treatment group, for the immunotherapy (c) and targeted therapy (d) groups compared to the chemotherapy group, while controlling for covariates” were not rejected.

Age had no significant relationship with ED visit payment status (OR=0.964; 95% CI: 0.925 to 1.004; Wald Chi-square=3.1134; p=0.0777). Compared to females, males were 15.5% more likely to have ED visit payments (OR=1.155; 95% CI: 0.741 to 1.801; Wald Chi-square=0.4055; p=0.5243). Compared to Whites, African Americans were 1.7% less likely to have ED visit payments (OR=0.983; 95% CI: 0.566 to 1.708; Wald Chi-square=0.0036; p=0.9522); Hispanics were 29.5% less likely to have ED visit payments (OR=0.705; 95% CI: 0.361 to 1.381; Wald Chi-square=1.0373; p=0.3085); and others were 27.5% more likely to have ED visit payments (OR=1.275; 95% CI: 0.681 to 2.386; Wald Chi-square=0.5755; p=0.4481). Compared to patients living in urban areas, patients living in rural areas were 43.7% less likely to have ED visit payments (OR=0.563; 95% CI: 0.355 to 0.892; Wald Chi-square=5.9813; p=0.0145). Compared to patients without comorbidities (CCI=0), patients with CCI=1 were 14.4% more likely

to have ED visit payments (OR=1.144; 95% CI: 0.641 to 2.041; Wald Chi-square=0.2059; p=0.6500), while patients with CCI=2 were 11.0% more likely to have ED visit payments (OR=1.110; 95% CI: 0.583 to 2.113; Wald Chi-square=0.1000; p=0.7518), and patients with CCI ≥ 3 were 65.3% more likely to have ED visit payments (OR=1.653; 95% CI: 0.777 to 3.519; Wald Chi-square=1.7017; p=0.1921). All results were while controlling for covariates.

Table 3.12 Logistic regression evaluating ED payment status (dichotomous)*

Variables	Estimate	Wald Chi-Square	P value	OR	Wald 95% Confidence Limits	
Treatment group (ref=Chemotherapy)						
Immunotherapy	0.0991	0.0806	0.7765	1.104	0.557	2.189
Targeted therapy	-0.1439	0.1277	0.7208	0.866	0.393	1.907
Age						
18-63 years old	-0.0371	3.1134	0.0777	0.964	0.925	1.004
Gender (ref=Female)						
Male	0.1442	0.4055	0.5243	1.155	0.741	1.801
Race (ref=White)						
African American	-0.0169	0.0036	0.9522	0.983	0.566	1.708
Hispanic	-0.3489	1.0373	0.3085	0.705	0.361	1.381
Others	0.2427	0.5755	0.4481	1.275	0.681	2.386
Area (ref=Urban)						
Rural	-0.5745	5.9813	0.0145	0.563	0.355	0.892
CCI (ref=0)						
1	0.1341	0.2059	0.6500	1.144	0.641	2.041
2	0.1039	0.1000	0.7518	1.110	0.583	2.113
≥3	0.5028	1.7017	0.1921	1.653	0.777	3.519
Intercept	3.1503	6.8069	0.0091			

* 0=no payments and 1=payments >\$0; ED = Emergency department

3.6.3 Office visit payment status

Logistic regression results evaluating office visit payment status are shown in Table 3.13. Compared to the chemotherapy group, the immunotherapy group was 322.4% more likely to have office visit payments (OR=4.224; 95% CI: 1.441 to 12.385; Wald Chi-square=6.8934; p=0.0087), while the targeted therapy group was 28.6% less likely to have office visit payments (OR=0.714; 95% CI: 0.325 to 1.567; Wald Chi-square=0.7062; p=0.4007), while controlling for other covariates. Thus, “H_{04e-f}: There are no significant relationships in lung cancer-related office visit payment status by treatment group, for the immunotherapy (e) and targeted therapy (f) groups compared to the chemotherapy group, while controlling for covariates” was rejected for H_{04e} (immunotherapy group) but not rejected for H_{04f} (targeted therapy group).

For every one-year increase in age, the odds of having office visit payments increased 6.8% (OR=1.068; 95% CI: 1.028 to 1.109; Wald Chi-square=11.6302; p=0.0006). Compared to females, males were 29.5% less likely to have office visit payments (OR=0.709; 95% CI: 0.440 to 1.130; Wald Chi-square=2.1140; p=0.1460). Compared to Whites, African Americans were 29.1% less likely to have office visit payments (OR=0.709; 95% CI: 0.397 to 1.264; Wald Chi-square=1.3612; p=0.2433); Hispanics were 36.2% less likely to have office visit payments (OR=0.638; 95% CI: 0.313 to 1.299; Wald Chi-square=1.5361; p=0.2152); and others were 20.6% more likely to have office payments (OR=1.206; 95% CI: 0.610 to 2.385; Wald Chi-square=0.2890; p=0.5908). Compared to patients living in urban areas, patients living in rural areas were 32.6% less likely to have office visit payments (OR=0.674; 95% CI: 0.409 to 1.112; Wald Chi-square=2.3838; p=0.1226). Compared to patients without comorbidities (CCI=0), patients with a CCI=1 were 154.7% more likely to have office visit payments (OR=2.547; 95% CI: 1.418 to 4.576; Wald Chi-square=9.7796; p=0.0018); patients with a CCI score=2 were 165.1% more likely to have office

visit payments (OR=2.651; 95% CI: 1.332 to 5.275; Wald Chi-square=7.7135; p=0.0055); and patients with a CCI score ≥ 3 were 134.3% more likely to have office visit payments (OR=2.343; 95% CI: 1.113 to 4.936; Wald Chi-square=5.0199; p=0.0251). All results were while controlling for covariates.

Table 3.13 Logistic regression evaluating office payment status (dichotomous)*

Variables	Estimate	Wald Chi-Square	P value	OR	Wald 95% Confidence Limits	
Treatment group (ref=Chemotherapy)						
Immunotherapy	1.4408	6.8934	0.0087	4.224	1.441	12.385
Targeted therapy	-0.3371	0.7062	0.4007	0.714	0.325	1.567
Age						
18-63 years old	0.0659	11.6302	0.0006	1.068	1.028	1.109
Gender (ref=Female)						
Male	-0.3499	2.1140	0.1460	0.705	0.440	1.130
Race (ref=White)						
African American	-0.3445	1.3612	0.2433	0.709	0.397	1.264
Hispanic	-0.4497	1.5361	0.2152	0.638	0.313	1.299
Others	0.1871	0.2890	0.5908	1.206	0.610	2.385
Area (ref=Urban)						
Rural	-0.3939	2.3838	0.1226	0.674	0.409	1.112
CCI (ref=0)						
1	0.9350	9.7796	0.0018	2.547	1.418	4.576
2	0.9749	7.7135	0.0055	2.651	1.332	5.275
≥3	0.8516	5.0199	0.0251	2.343	1.113	4.936
Intercept	-2.9280	7.1624	0.0074			

* 0=no payments and 1=payments >\$0

3.6.4 Hospital outpatient visit payment status

Logistic regression results evaluating hospital outpatient visit payment status are shown in Table 3.14. Compared to the chemotherapy group, the immunotherapy group was 116.8% more likely to have hospital outpatient visit payments (OR=2.168; 95% CI: 0.927 to 5.069; Wald Chi-square=3.1903; p=0.0741); and the targeted therapy group was 5.8% less likely to have hospital outpatient visit payments (OR=0.942; 95% CI: 0.421 to 2.110; Wald Chi-square=0.0210; p=0.8847), while controlling for other covariates. However, these relationships were not significant. Thus, “H₀4g-h: There are no significant relationships in lung cancer-related hospital outpatient visit payment status by treatment group, for the immunotherapy (g) and targeted therapy (h) groups compared to the chemotherapy group, while controlling for covariates” were not rejected.

For every one-year increase in age, the odds of having a hospital outpatient visit payment increased 3.6% (OR=1.036; 95% CI: 0.999 to 1.075; Wald Chi-square=3.7286; p=0.0535). Compared to females, males were 1.4% less likely to have hospital outpatient visit payments (OR=0.986; 95% CI: 0.621 to 1.565; Wald Chi-square=0.0036; p=0.9521). Compared to Whites, African Americans were 15.8% less likely to have hospital outpatient visit payments (OR=0.842; 95% CI: 0.471 to 1.504; Wald Chi-square=0.3374; p=0.5613); Hispanics were 48.9% less likely to have hospital outpatient visit payments (OR=0.511; 95% CI: 0.262 to 0.999; Wald Chi-square=3.8555; p=0.0496); and others were 7.0% more likely to have hospital outpatient visit payments (OR=1.070; 95% CI: 0.558-2.052; Wald Chi-square=0.0410; p=0.8395). Compared to patients living in urban areas, patients living in rural areas were 68.8% more likely to have a hospital outpatient visit payment (OR=1.688; 95% CI: 0.992 to 2.871; Wald Chi-square=3.7249; p=0.0536). Compared to patients without comorbidities, patients with a CCI=1 were 68.1% more

likely to have hospital outpatient visit payments (OR=1.681; 95% CI: 0.943 to 2.997; Wald Chi-square=3.0992; p=0.0783); patients with a CCI score=2 were 65.2% more likely to have hospital outpatient visit payments (OR=1.652; 95% CI: 0.853 to 3.199; Wald Chi-square=2.2166; p=0.1365); and patients with a CCI score ≥ 3 were 116.8% more likely to have hospital outpatient visit payments (OR=2.168; 95% CI: 0.999 to 4.701; Wald Chi-square=3.8348; p=0.0502). All results were while controlling for covariates.

Table 3.14 Logistic regression evaluating hospital outpatient visit payment status (dichotomous)*

Variables	Estimate	Wald Chi-Square	P value	OR	Wald 95% Confidence Limits	
Treatment group (ref=Chemotherapy)						
Immunotherapy	0.7739	3.1903	0.0741	2.168	0.927	5.069
Targeted therapy	-0.0597	0.0210	0.8847	0.942	0.421	2.110
Age						
18-63 years old	0.0357	3.7286	0.0535	1.036	0.999	1.075
Gender (ref=Female)						
Male	-0.0142	0.0036	0.9521	0.986	0.621	1.565
Race (ref=White)						
African American	-0.1720	0.3374	0.5613	0.842	0.471	1.504
Hispanic	-0.6706	3.8555	0.0496	0.511	0.262	0.999
Others	0.0673	0.0410	0.8395	1.070	0.558	2.052
Area (ref=Urban)						
Rural	0.5233	3.7249	0.0536	1.688	0.992	2.871
CCI (ref=0)						
1	0.5193	3.0992	0.0783	1.681	0.943	2.997
2	0.5019	2.2166	0.1365	1.652	0.853	3.199
≥3	0.7736	3.8348	0.0502	2.168	0.999	4.701
Intercept	-1.3556	1.6688	0.1964			

* 0=no payments and 1=payments >\$0

3.6.5 Home visit payment status

Logistic regression results evaluating home visit payment status are shown in Table 3.15. Compared to the chemotherapy group, the immunotherapy group was 56.5% more likely to have home visit payments (OR=1.565; 95% CI: 0.832 to 2.944; Wald Chi-square=1.9308; p=0.1647); and the targeted therapy group was 4.4% less likely to have home visit payments (OR=0.956; 95% CI: 0.414 to 2.209; Wald Chi-square=0.0112; p=0.9156), while controlling for other covariates. However, these relationships were not significant. Thus, “H₀4i-j: There are no significant relationships in lung cancer-related home visit payment status by treatment group, for the immunotherapy (i) and targeted therapy (j) groups compared to the chemotherapy group, while controlling for covariates” were not rejected.

For every one-year increase in age, the odds of having a home visit payment increased 2.0% (OR=1.020; 95% CI: 0.980 to 1.062; Wald Chi-square=0.9402; p=0.3322). Compared to females, males were 4.8% more likely to have home visit payments (OR=1.048; 95% CI: 0.672 to 1.632; Wald Chi-square=0.0421; p=0.8374). Compared to Whites, African Americans were 44.7% more likely to have home visit payments (OR=1.447; 95% CI: 0.841 to 2.490; Wald Chi-square=1.7780; p=0.1824); Hispanics were 8.7% less likely to have home visit payments (OR=0.913; 95% CI: 0.439 to 1.898; Wald Chi-square=0.0598; p=0.8068); and others were 12.8% more likely to have home visit payments (OR=1.128; 95% CI: 0.617 to 2.061; Wald Chi-square=0.1532; p=0.6955). Compared to patients living in urban areas, patients living in rural areas were 28.6% less likely to have home visit payments (OR=0.714; 95% CI: 0.435-1.170; Wald Chi-square=1.7900; p=0.1809). Compared to patients without comorbidities, patients with CCI=1 were 31.8% more likely to have home visit payments (OR=1.318; 95% CI: 0.721 to 2.412; Wald Chi-square=0.8048; p=0.3697); patients with a CCI score=2 were 22.2% more likely to have home visit payments (OR=1.222; 95%

CI: 0.621 to 2.404; Wald Chi-square=0.3366; p=0.5618); and patients with a CCI score ≥ 3 were 18.3% more likely to have home visit payments (OR=1.183; 95% CI: 0.562 to 2.494; Wald Chi-square=0.1962; p=0.6578). All results were while controlling for covariates.

Table 3.15 Logistic regression evaluating home visit payment status (dichotomous)*

Variables	Estimate	Wald Chi-Square	P value	OR	Wald 95% Confidence Limits	
Treatment group (ref=Chemotherapy)						
Immunotherapy	0.4479	1.9308	0.1647	1.565	0.832	2.944
Targeted therapy	-0.0453	0.0112	0.9156	0.956	0.414	2.209
Age						
18-63 years old	0.0200	0.9402	0.3322	1.020	0.980	1.062
Gender (ref=Female)						
Male	0.0464	0.0421	0.8374	1.048	0.672	1.632
Race (ref=White)						
African American	0.3693	1.7780	0.1824	1.447	0.841	2.490
Hispanic	-0.0913	0.0598	0.8068	0.913	0.439	1.898
Others	0.1204	0.1532	0.6955	1.128	0.617	2.061
Area (ref=Urban)						
Rural	-0.3374	1.7900	0.1809	0.714	0.435	1.170
CCI (ref=0)						
1	0.2765	0.8048	0.3697	1.318	0.721	2.412
2	0.2003	0.3366	0.5618	1.222	0.621	2.404
≥3	0.1685	0.1962	0.6578	1.183	0.562	2.494
Intercept	-2.4927	4.4701	0.0345			

* 0=no payments and 1=payments >\$0

3.6.6 Other visit payment status

Logistic regression results evaluating other visit payment status are shown in Table 3.16. Compared to the chemotherapy group, the immunotherapy group was 197.4% more likely to have other visit payments (OR=2.974; 95% CI: 1.586 to 5.576; Wald Chi-square=11.5411; p=0.0007); and the targeted therapy group was 25.9% less likely to have other visit payments (OR=0.741; 95% CI: 0.352 to 1.557; Wald Chi-square=0.6265; p=0.4286), while controlling for other covariates. Thus, “H₀4k-l: There are no significant relationships in lung cancer-related other visit payment status by treatment group, for the immunotherapy (k) and targeted therapy (l) groups compared to the chemotherapy group, while controlling for covariates” was rejected for H₀4k (immunotherapy group) but not rejected for H₀4l (targeted therapy group).

For every one-year increase in age, the odds of having other visit payments increased 2.2% (OR=1.022; 95% CI: 0.988 to 1.058; Wald Chi-square=1.5861; p=0.2079). Compared to females, males were 15.4% less likely to have other visit payments (OR=0.846; 95% CI: 0.569 to 1.256; Wald Chi-square=0.6899; p=0.4062). Compared to Whites, African Americans were 10.6% less likely to have other visit payments (OR=0.894; 95% CI: 0.546 to 1.464; Wald Chi-square=0.1985; p=0.6559); Hispanics were 26.5% less likely to have other visit payments (OR=0.735; 95% CI: 0.390 to 1.386; Wald Chi-square=0.9024; p=0.3421); and others were 14.8% less likely to have other visit payments (OR=0.852; 95% CI: 0.498 to 1.455; Wald Chi-square=0.3452; p=0.5569). Compared to patients living in urban areas, patients living in rural areas were 32.4% less likely to have other visit payments (OR=0.676; 95% CI: 0.440 to 1.040; Wald Chi-square=3.1803; p=0.0745). Compared to patients without comorbidities, patients with CCI=1 were 79.8% more likely to have other visit payments (OR=1.798; 95% CI: 1.053 to 3.070; Wald Chi-square=4.6134; p=0.0317); patients with a CCI score=2 were 39.1% more likely to have other visit payments

(OR=1.391; 95% CI: 0.762 to 2.538; Wald Chi-square=1.1579; p=0.2819); and patients with a CCI score ≥ 3 were 53.6% more likely to have other visit payments (OR=1.536; 95% CI: 0.794 to 2.973; Wald Chi-square=1.6255; p=0.2023). All results were while controlling for covariates.

Table 3.16 Logistic regression evaluating other visit payment status (dichotomous)*

Variables	Estimate	Wald Chi-Square	P value	OR	Wald 95% Confidence Limits	
Treatment group (ref=Chemotherapy)						
Immunotherapy	1.0898	11.5411	0.0007	2.974	1.586	5.576
Targeted therapy	-0.3000	0.6265	0.4286	0.741	0.352	1.557
Age						
18-63 years old	0.0221	1.5861	0.2079	1.022	0.988	1.058
Gender (ref=Female)						
Male	-0.1677	0.6899	0.4062	0.846	0.569	1.256
Race (ref=White)						
African American	-0.1121	0.1985	0.6559	0.894	0.546	1.464
Hispanic	-0.3073	0.9024	0.3421	0.735	0.390	1.386
Others	-0.1606	0.3452	0.5569	0.852	0.498	1.455
Area (ref=Urban)						
Rural	-0.3912	3.1803	0.0745	0.676	0.440	1.040
CCI (ref=0)						
1	0.5865	4.6134	0.0317	1.798	1.053	3.070
2	0.3301	1.1579	0.2819	1.391	0.762	2.538
≥3	0.4295	1.6255	0.2023	1.536	0.794	2.973
Intercept	-1.6582	2.7286	0.0986			

* 0=no payments and 1=payments >\$0

3.6.7 Prescription payment status

Since only 15 patients had lung cancer-related prescriptions, logistic regression is not applicable for this analysis. No conclusions were made for H₀4o-p.

3.6.8 total payment status

Since nearly all patients (439, 96.9%) had payments >0, logistic regression is not applicable for this analysis. No conclusions were made for H₀4q-r.

3.7 Objective 5 Healthcare payments

For objective 5, generalized linear models (GLMs) with a gamma distribution and a log-link were used for analyses of payment data. These analyses used payments greater than 0. Before presenting these results, a brief summary of the payments for the overall population will be presented including the mean payments by health service types and treatment groups (Figure 3.3). This would be followed by the GLM results.

Descriptive analysis for overall population

The mean payments for the overall population by the types of healthcare utilization associated with treatment groups are displayed in Figure 3.3. Mean total payments were \$40,321 for the overall population. Mean total payments for the immunotherapy group (\$90,179) were much higher than for the chemotherapy group (\$34,620), while mean total payments for the targeted therapy (\$23,287) were lower than for the chemotherapy group (\$34,620). Office visit payments accounted for the majority of total costs in the overall population and in the treatment

groups in our study, consistent with the wide use of office visits. Office visit payments for the immunotherapy group (71%) and the targeted therapy group (69%) accounted for a higher proportion of total costs compared to the chemotherapy group (50%). Hospital outpatient visit payments accounted for 19% to 32% of total costs, with the highest proportion in the chemotherapy group and the lowest proportion in the targeted and immunotherapy groups. Hospitalization payments accounted for 14% of total payments in the chemotherapy group, but only 5% and 8% of total payments in the immunotherapy group and targeted therapy group, respectively. The proportions of total payments accounted for by ED visits, home visits and other visits were low. Payments by types of healthcare resources are presented in detail below.

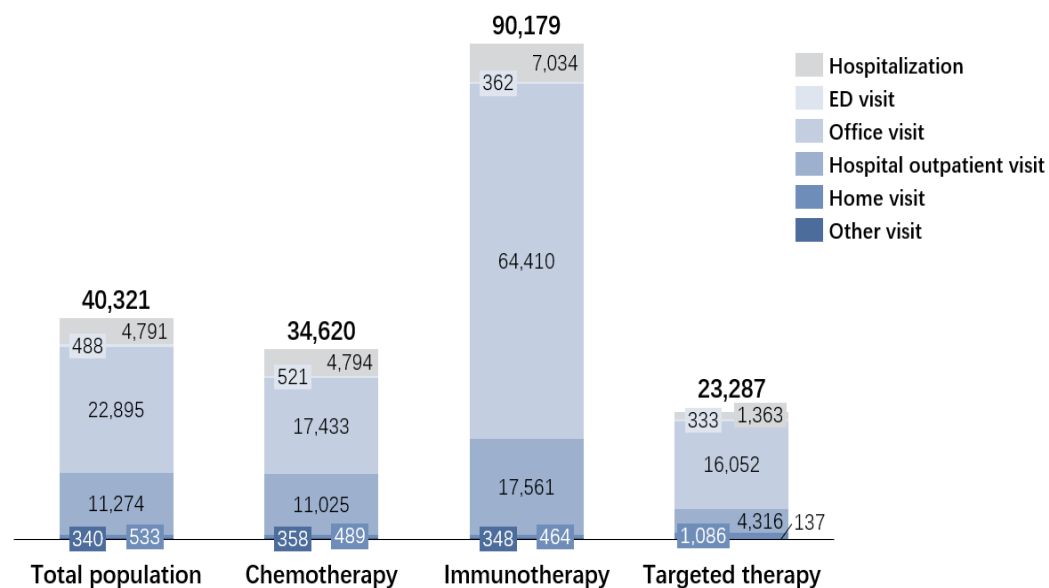


Figure 3.3 The breakdown of total mean costs by health services and treatment groups (\$)

GLM analysis

Because the payment data were positively skewed, generalized linear models (GLMs) with a gamma distribution and a log-link were used for analyses of payment data. The results for the treatment variable are interpreted with covariates=0. The results for covariates are interpreted for treatment group=0 (chemotherapy) and all other covariates=0. To yield mean payment estimates for other values of the treatment group and covariates, the exponentiated estimate of the intercept should be multiplied by the corresponding exponentiated estimate for each variable/category.

3.7.1 Hospitalization payments

Based on descriptive analyses, the mean (SD) hospitalization payment for the overall population was \$4,791 (\$14,270), with \$4,794 (\$14,467) for the chemotherapy group, \$7,034 (\$16,449) for the immunotherapy group, and \$1,363 (\$5,801) for the targeted therapy group. The results from the GLM evaluating hospitalization payments are shown in Table 3.17. Only 15% (70 patients) of the study sample had inpatient visits. Compared to the chemotherapy group, the immunotherapy group had 6% lower hospitalization payments (exponentiated estimate=0.9400, 95% CI: 0.6111 to 1.4457, $p=0.7779$) with an estimated mean of \$3,373 ($3,589 \times 0.9400$), while the targeted therapy group had 8.44% lower hospitalization payments (exponentiated estimate=0.9156, 95% CI: 0.6440 to 1.3015, $p=0.623$) with an estimated mean of \$3,286 ($3,589 \times 0.9156$), with reference groups for covariates=0. However, these relationships were not significant. Thus, “H₀5a-b: There are no significant relationships in the mean lung cancer-related hospitalization payments by treatment group, for the immunotherapy (a) and targeted therapy (b) groups compared to the chemotherapy group, while controlling for covariates” were not rejected.

With respect to the covariates, for every one-year increase in age, the hospitalization payment significantly increased 3.75% (exponentiated estimate=1.0375, 95% CI: 1.0064 to 1.0694, $p=0.0176$). Compared to females, males had 13.93% higher hospitalization payments (exponentiated estimate=1.1393, 95% CI: 0.8133 to 1.5960, $p=0.4482$) with an estimated mean of \$4,089 ($3,589 \times 1.1393$). Compared to Whites, African Americans had 3.62% lower hospitalization payments (exponentiated estimate=0.9638, 95% CI: 0.6209 to 1.4962, $p=0.8695$) with an estimated mean of \$3,499 ($3,589 \times 0.9638$); Hispanics had 8.49% higher hospitalization payments (exponentiated estimate=1.0849, 95% CI: 0.5085 to 2.3147, $p=0.833$) with an estimated mean of \$3,894 ($3,589 \times 1.0849$); and others had 51.06% higher hospitalization payments (exponentiated estimate=1.5106, 95% CI: 1.0186 to 2.2405, $p=0.0402$) with an estimated mean of \$5,422 ($3,589 \times 1.5106$). Compared to patients living in urban areas, patients living in rural areas had 22.61% lower hospitalization payments (exponentiated estimate=0.7739, 95% CI: 0.5556 to 1.0781, $p=0.1297$) with an estimated mean of \$2,778 ($3,589 \times 0.7739$). Compared to patients without comorbidities, patients with CCI=1 had 1.84% lower hospitalization payments (exponentiated estimate=0.9816, 95% CI: 0.5641 to 1.7081, $p=0.9475$) with an estimated mean of \$3,523 ($3,589 \times 0.9816$); patients with a CCI score=2 had 12.41% lower hospitalization payments (exponentiated estimate=0.8759, 95% CI: 0.4737 to 1.6195, $p=0.6726$) with an estimated mean of \$3,144 ($3,589 \times 0.8759$); and patients with a CCI score ≥ 3 had 4.87% lower hospitalization payments (exponentiated estimate=0.9513, 95% CI: 0.5629 to 1.6077, $p=0.852$) with an estimated mean of \$3,414 ($3,589 \times 0.9513$). All results are for treatment group=0 (chemotherapy) and all other covariates=0.

Table 3.17 GLM regression evaluating hospitalization payments (continuous)

Variables	Exp Estimate	Estimate	Standard Error	95% Confidence Limits		Z	P value
Treatment group (ref=Chemotherapy)							
Immunotherapy	0.9400	-0.0619	0.2197	0.6111	1.4457	-0.28	0.7779
Targeted therapy	0.9156	-0.0882	0.1795	0.6440	1.3015	-0.49	0.623
Age							
18-63 years old	1.0375	0.0368	0.0155	1.0064	1.0694	2.37	0.0176
Gender (ref=Female)							
Male	1.1393	0.1304	0.172	0.8133	1.5960	0.76	0.4482
Race (ref=White)							
African American	0.9638	-0.0369	0.2244	0.6209	1.4962	-0.16	0.8695
Hispanic	1.0849	0.0815	0.3866	0.5085	2.3147	0.21	0.833
Others	1.5106	0.4125	0.2011	1.0186	2.2405	2.05	0.0402
Area (ref=Urban)							
Rural	0.7739	-0.2563	0.1691	0.5556	1.0781	-1.52	0.1297
CCI (ref=0)							
1	0.9816	-0.0186	0.2827	0.5641	1.7081	-0.07	0.9475
2	0.8759	-0.1325	0.3136	0.4737	1.6195	-0.42	0.6726
≥3	0.9513	-0.0499	0.2678	0.5629	1.6077	-0.19	0.8520
Intercept	3588.5374	8.1855	0.83	705.3541	18256.9298	9.86	<.0001

Note: Exp= Exponentiated

3.7.2 ED visit payments

Based on descriptive analyses, the mean (SD) ED visit payment for the overall population was \$488 (\$796), with \$521 (\$854) for the chemotherapy group, \$362 (\$491) for the immunotherapy group, and \$333 (\$453) for the targeted therapy group. The results from the GLM evaluating ED payments are shown in Table 3.18. A total of 330 (72.85%) patients had ED visits during the follow-up period. Compared to the chemotherapy group, the immunotherapy group had 31.31% lower ED visit payments (exponentiated estimate=0.6869, 95% CI: 0.4718 to 1.0000,

p=0.05) with an estimated mean of \$974 ($1,418 \times 0.6869$), while the targeted therapy group had a 23.77% lower ED visit payment (exponentiated estimate=0.7623, 95% CI: 0.4765 to 1.2195, p=0.2575) with an estimated mean of \$1,081 ($1,418 \times 0.7623$). Thus, “H₀5c-d: There are no significant relationships in the mean lung cancer-related ED visit payments by treatment group, for the immunotherapy (c) and targeted therapy (d) groups compared to the chemotherapy group, while controlling for covariates” was rejected for H₀5c (immunotherapy group) but not rejected for H₀5d (targeted therapy group).

For every one-year increase in age, the ED visit payment decreased 1.94% (exponentiated estimate=0.9806, 95% CI: 0.9644 to 0.9971, p=0.0211). Compared to females, males had 12.61% lower ED visit payments (exponentiated estimate=0.8739, 95% CI: 0.6640 to 1.1500, p=0.336) with an estimated mean of \$1,239 ($1,418 \times 0.8739$). Compared to Whites, African Americans had 41.28% higher ED visit payments (exponentiated estimate=1.4128, 95% CI: 0.9726 to 2.0526, p=0.0697) with an estimated mean of \$2,003 ($1,418 \times 1.4128$); Hispanics had 54.45% higher ED visit payments (exponentiated estimate=1.5445, 95% CI: 1.1109 to 2.1471, p=0.0097) with an estimated mean of \$2,190 ($1,418 \times 1.5445$); and others had 59.63% higher ED visit payments (exponentiated estimate=1.5963, 95% CI: 1.1637 to 2.1898, p=0.0037) with an estimated mean of \$2,264 ($1,418 \times 1.5963$). Compared to patients living in urban areas, patients living in rural areas had 0.23% lower ED visit payments (exponentiated estimate=0.9977, 95% CI: 0.7447 to 1.3367, p=0.9875) with an estimated mean of \$1,415 ($1,418 \times 0.9977$). Compared to patients without comorbidities, patients with a CCI score of 1 had 11.47% higher ED visit payments (exponentiated estimate=1.1147, 95% CI: 0.8490 to 1.4635, p=0.4345) with an estimated mean of \$1,581 ($1,418 \times 1.1147$); patients with a CCI score=2 had 47.36% higher ED visit payments (exponentiated estimate=1.4736, 95% CI: 0.9659 to 2.2484, p=0.072) with an estimated mean of \$2,090

(1,418*1.4736); and patients with a CCI score ≥ 3 had 31.01% higher ED visit payments (exponentiated estimate=1.3101, 95% CI: 0.8241 to 2.0828, p=0.2534) with an estimated mean of \$1,858 (1,418*1.3101). All results are for treatment group=0 (chemotherapy) and all other covariates=0.

Table 3.18 GLM regression evaluating ED visit payments (continuous)

Variables	Exp Estimate	Estimate	Standard Error	95% Confidence Limits		Z	P value
Treatment group (ref=Chemotherapy)							
Immunotherapy	0.6869	-0.3756	0.1916	0.4718	1.0000	-1.96	0.05
Targeted therapy	0.7623	-0.2714	0.2397	0.4765	1.2195	-1.13	0.2575
Age							
18-63 years old	0.9806	-0.0196	0.0085	0.9644	0.9971	-2.31	0.0211
Gender (ref=Female)							
Male	0.8739	-0.1348	0.1401	0.6640	1.1500	-0.96	0.336
Race (ref=White)							
African American	1.4128	0.3456	0.1906	0.9726	2.0526	1.81	0.0697
Hispanic	1.5445	0.4347	0.1681	1.1109	2.1471	2.59	0.0097
Others	1.5963	0.4677	0.1613	1.1637	2.1898	2.9	0.0037
Area (ref=Urban)							
Rural	0.9977	-0.0023	0.1492	0.7447	1.3367	-0.02	0.9875
CCI (ref=0)							
1	1.1147	0.1086	0.1389	0.8490	1.4635	0.78	0.4345
2	1.4736	0.3877	0.2155	0.9659	2.2484	1.8	0.072
≥3	1.3101	0.1086	0.1389	0.8241	2.0828	1.14	0.2534
Intercept	1417.7126	7.2568	0.5004	531.6578	3780.4563	14.5	<.0001

Note: Exp= Exponentiated

3.7.3 Office visit payments

Based on descriptive analyses, the mean (SD) office visit payment for the overall population was \$22,895 (\$38,242), with \$17,433 (\$27,897) for the chemotherapy group, \$64,410 (\$67,147) for the immunotherapy group, and \$16,052 (\$32,305) for the targeted therapy group. The results from the GLM evaluating office visit payments are shown in Table 3.19. A total of 338 (74.6%) patients had office visits during the follow-up period. Compared to the chemotherapy group, the immunotherapy group had 218.96% higher office visit payments (exponentiated estimate=3.1896, 95% CI: 2.3226 to 4.3798, $p<0.0001$) with an estimated mean of \$39,482 ($12,378 \times 3.1896$), while the targeted therapy group had 6.39% lower office visit payments (exponentiated estimate=0.9361, 95% CI: 0.5124 to 1.7102, $p=0.83$) with an estimated mean of \$11,588 ($12,378 \times 0.9361$). Thus, “H₀5e-f: There are no significant relationships in the mean lung cancer-related office visit payments by treatment group, for the immunotherapy (e) and targeted therapy (f) groups compared to the chemotherapy group, while controlling for covariates” was rejected for H₀5e (immunotherapy group) but not rejected for H₀5f (targeted therapy group).

For every one-year increase in age, the office visit payment increased 0.86% (exponentiated estimate=1.0086, 95% CI: 0.9774 to 1.0409, $p=0.5915$). Compared to females, males had 35.22% higher office visit payments (exponentiated estimate=1.3522, 95% CI: 1.0362 to 1.7644, $p=0.0263$) with an estimated mean of \$16,738 ($12,378 \times 1.3522$). Compared to Whites, African Americans had 19.11% lower office visit payments (exponentiated estimate=0.8089, 95% CI: 0.5779 to 1.1320, $p=0.2161$) with an estimated mean of \$10,013 ($12,378 \times 0.8089$); Hispanics had 35.37% lower office visit payments (exponentiated estimate=0.6463, 95% CI: 0.4315 to 0.9679, $p=0.0341$) with an estimated mean of \$8,000 ($12,378 \times 0.6463$); and others had 25.63% lower office visit payments (exponentiated estimate=0.7437, 95% CI: 0.5196 to 1.0645, $p=0.1056$).

with an estimated mean of \$9,206 ($12,378 \times 0.7437$). Compared to patients living in urban areas, patients living in rural areas had 4.07% lower office visit payments (exponentiated estimate=0.9593, 95% CI: 0.7268 to 1.2663, $p=0.7694$) with an estimated mean of \$11,874 ($12,378 \times 0.9593$). Compared to patients without comorbidities, patients with a CCI score of 1 had 24.63% higher office visit payments (exponentiated estimate=1.2463, 95% CI: 0.8571 to 1.8123, $p=0.249$) with an estimated mean of \$15,427 ($12,378 \times 1.2463$); patients with a CCI score of 2 had 14.89% higher office visit payments (exponentiated estimate=1.1489, 95% CI: 0.7504 to 1.7587, $p=0.523$) with an estimated mean of \$14,221 ($12,378 \times 1.1489$); and patients with a CCI score ≥ 3 had 30.71% higher office visit payments (exponentiated estimate=1.3071, 95% CI: 0.8306 to 2.0571, $p=0.247$) with an estimated mean of \$16,179 ($12,378 \times 1.3071$). All results are for treatment group=0 (chemotherapy) and all other covariates=0.

Table 3.19 GLM regression evaluating office visit payments (continuous)

Variables	Exp Estimate	Estimate	Standard Error	95% Confidence Limits		Z	P value
Treatment group (ref=Chemotherapy)							
Immunotherapy	3.1896	1.1599	0.1618	2.3226	4.3798	7.17	<.0001
Targeted therapy	0.9361	-0.066	0.3074	0.5124	1.7102	-0.21	0.83
Age							
18-63 years old	1.0086	0.0086	0.0161	0.9774	1.0409	0.54	0.5915
Gender (ref=Female)							
Male	1.3522	0.3017	0.1358	1.0362	1.7644	2.22	0.0263
Race (ref=White)							
African American	0.8089	-0.2121	0.1715	0.5779	1.1320	-1.24	0.2161
Hispanic	0.6463	-0.4365	0.2061	0.4315	0.9679	-2.12	0.0341
Others	0.7437	-0.2961	0.1829	0.5196	1.0645	-1.62	0.1056
Area (ref=Urban)							
Rural	0.9593	-0.0415	0.1416	0.7268	1.2663	-0.29	0.7694
CCI (ref=0)							
1	1.2463	0.2202	0.191	0.8571	1.8123	1.15	0.249
2	1.1489	0.1388	0.2173	0.7504	1.7587	0.64	0.523
≥3	1.3071	0.2678	0.2314	0.8306	2.0571	1.16	0.247
Intercept	12,378	9.4237	0.9326	1990.0201	76995.3262	10.1	<.0001

Note: Exp= Exponentiated

3.7.4 Hospital Outpatient Visit Payments

Based on descriptive analyses, the mean (SD) hospital outpatient visit payment for the overall population was \$11,274 (\$28,855), with \$11,025 (\$26,593) for the chemotherapy group, \$17,561 (\$45,792) for the immunotherapy group, and \$4,316 (\$12,500) for the targeted therapy group. The results from the GLM evaluating hospital outpatient visit payments are shown in Table

3.20. A total of 305 (67.3%) patients had hospital outpatient visit payments. Compared to the chemotherapy group, the immunotherapy group had 13.37% higher hospital outpatient visit payments (exponentiated estimate=1.1337, 95% CI: 0.6151 to 2.0894, $p<0.6875$) with an estimated mean of \$324,779 ($286,473 \times 1.1337$); while the targeted therapy group had 47.86% lower hospital outpatient visit payments (exponentiated estimate=0.5214, 95% CI: 0.2299 to 1.1828, $p=0.1192$) with an estimated mean of \$149,373 ($286,473 \times 0.5214$). However, these relationships were not significant. Thus, “H_{05g-h}: There are no significant relationships in the mean lung cancer-related hospital outpatient visit payments by treatment group, for the immunotherapy (g) and targeted therapy (h) groups compared to the chemotherapy group, while controlling for covariates” were not rejected.

For every one-year increase in age, hospital outpatient visit payments decreased by 5.47% (exponentiated estimate=0.9453, 95% CI: 0.9067 to 0.9854, $p=0.008$). Compared to females, males had 11.08% higher hospital outpatient visit payments (exponentiated estimate=1.1108, 95% CI: 0.7289 to 1.6928, $p=0.6248$) with an estimated mean of \$318,221 ($286,473 \times 1.1108$). Compared to Whites, African Americans had 71.29% higher hospital outpatient visit payments (exponentiated estimate=1.7129, 95% CI: 1.0434 to 2.8123, $p=0.0333$) with an estimated mean of \$490,706 ($286,473 \times 1.7129$); Hispanics had 71.38% lower hospital outpatient visit payments (exponentiated estimate=0.2862, 95% CI: 0.1478 to 0.5543, $p=0.0002$) with an estimated mean of \$81,986 ($286,473 \times 0.2862$); and others had 63.97% higher hospital outpatient visit payments (exponentiated estimate=1.6397, 95% CI: 0.9326 to 2.8832, $p=0.0859$) with an estimated mean of \$469,724 ($286,473 \times 1.6397$). Compared to patients living in urban areas, patients living in rural areas had 46.91% lower hospital outpatient visit payments (exponentiated estimate=0.5309, 95% CI: 0.3317 to 0.8497, $p=0.0083$) with an estimated mean of \$152,086 ($286,473 \times 0.5309$).

Compared to patients without comorbidities, patients with a CCI score of 1 had 16.98% higher hospital outpatient visit payments (exponentiated estimate=1.1698, 95% CI: 0.6417 to 2.1327, $p=0.6088$) with an estimated mean of \$335,105 ($286,473 \times 1.1698$); patients with a CCI score of 2 had 40.96% higher hospital outpatient visit payments (exponentiated estimate=1.4096, 95% CI: 0.7280 to 2.7294, $p=0.3085$) with an estimated mean of \$403,810 ($286,473 \times 1.4096$); and patients with a CCI score ≥ 3 had 12.36% higher hospital outpatient visit payments (exponentiated estimate=1.1236, 95% CI: 0.5625 to 2.2445, $p=0.7414$) with an estimated mean of \$321,869 ($286,473 \times 1.1236$). All results are for treatment group=0 (chemotherapy) and all other covariates=0.

Table 3.20 GLM regression evaluating hospital outpatient visit payments (continuous)

Variables	Exp Estimate	Estimate	Standar rd Error	Confidence Limits		Z	P value
Treatment group (ref=Chemotherapy)							
Immunotherapy	1.1337	0.1255	0.312	0.6151	2.0894	0.4	0.6875
Targeted therapy	0.5214	-0.6512	0.4179	0.2299	1.1828	-1.56	0.1192
Age							
18-63 years old	0.9453	-0.0563	0.0212	0.9067	0.9854	-2.65	0.008
Gender (ref=Female)							
Male	1.1108	0.1051	0.215	0.7289	1.6928	0.49	0.6248
Race (ref=White)							
African American	1.7129	0.5382	0.2529	1.0434	2.8123	2.13	0.0333
Hispanic	0.2862	-1.2511	0.3372	0.1478	0.5543	-3.71	0.0002
Others	1.6397	0.4945	0.2879	0.9326	2.8832	1.72	0.0859
Area (ref=Urban)							
Rural	0.5309	-0.6332	0.24	0.3317	0.8497	-2.64	0.0083
CCI (ref=0)							
1	1.1698	0.1568	0.3064	0.6417	2.1327	0.51	0.6088
2	1.4096	0.3433	0.3371	0.7280	2.7294	1.02	0.3085
≥3	1.1236	0.1165	0.3531	0.5625	2.2445	0.33	0.7414
Intercept	286473.1232	12.5654	1.2486	24787.6296	3310467.5793	10.06	<.0001

Note: Exp= Exponentiated

3.7.5 Home Visit Payments

Based on descriptive analyses, the mean (SD) home visit payment for the overall population was \$533 (\$2,431), with \$489 (\$2,352) for the chemotherapy group, \$464 (\$1,213) for the immunotherapy group, and \$1,086 (\$4,080) for the targeted therapy group. The results from the GLM evaluating home visit payments are shown in Table 3.21. A total of 112 (24.7%) patients

had home visit payments. Compared to the chemotherapy group, the immunotherapy group had 23.26% lower home visit payments (exponentiated estimate=0.7674, 95% CI: 0.3863 to 1.5244, $p=0.4496$) with an estimated mean of \$7,188 ($9,367 \times 0.7674$); while the targeted therapy group had 131.89% higher home visit payments (exponentiated estimate=2.3189, 95% CI: 0.7864 to 6.8373, $p=0.1274$) with an estimated mean of \$21,720 ($9,367 \times 2.3189$). However, these relationships were not significant. Thus, “H₀5i-j: There are no significant relationships in the mean lung cancer-related home visit payments by treatment group, for the immunotherapy (i) and targeted therapy (j) groups compared to the chemotherapy group, while controlling for covariates” were not rejected.

For every one-year increase in age, the home visit payment decreased 3.54% (exponentiated estimate=0.9646, 95% CI: 0.9282 to 1.0025, $p=0.0666$). Compared to females, males had 11.35% lower home visit payments (exponentiated estimate=0.8865, 95% CI: 0.4742 to 1.6575, $p=0.706$) with an estimated mean of \$8,303 ($9,367 \times 0.8865$). Compared to Whites, African Americans had 34.61% higher home visit payments (exponentiated estimate=1.3461, 95% CI: 0.5637 to 3.2143, $p=0.5035$) with an estimated mean of \$12,608 ($9,367 \times 1.3461$); Hispanics had 142.10% higher home visit payments (exponentiated estimate=2.4210, 95% CI: 0.8186 to 7.1599, $p=0.11$) with an estimated mean of \$22,677 ($9,367 \times 2.4210$); and others had 10.96% higher home visit payments (exponentiated estimate=1.1096, 95% CI: 0.4326 to 2.8457, $p=0.8287$) with an estimated mean of \$10,393 ($9,367 \times 1.1096$). Compared to patients living in urban areas, patients living in rural areas had 14.57% lower home visit payments (exponentiated estimate=0.8543, 95% CI: 0.4167 to 1.7512, $p=0.6672$) with an estimated mean of \$8,002 ($9,367 \times 0.8543$). Compared to patients without comorbidities, patients with a CCI score of 1 had 20.36% higher home visit payments (exponentiated estimate=1.2036, 95% CI: 0.5512 to 2.6279, $p=0.6418$) with an estimated mean of \$11,274 ($9,367 \times 1.2036$); patients with a CCI score of 2 had 171.91% higher

home visit payments (exponentiated estimate=2.7191, 95% CI: 1.1714 to 6.3117, p=0.0199) with an estimated mean of \$25,469 (9,367*2.7191); and patients with a CCI score ≥ 3 had 50.49% lower home visit payments (exponentiated estimate=0.4951, 95% CI: 0.2106 to 1.1642, p=0.1071) with an estimated mean of \$4,637 (9,367*0.4951). All results are for treatment group=0 (chemotherapy) and all other covariates=0.

Table 3.21 GLM regression evaluating home visit payments (continuous)

Variables	Exp Estimate	Estimate	Standard Error	95% Confidence Limits		Z	P value
Treatment group (ref=Chemotherapy)							
Immunotherapy	0.7674	-0.2648	0.3502	0.3863	1.5244	-0.76	0.4496
Targeted therapy	2.3189	0.8411	0.5517	0.7864	6.8373	1.52	0.1274
Age							
18-63 years old	0.9646	-0.036	0.0196	0.9282	1.0025	-1.83	0.0666
Gender (ref=Female)							
Male	0.8865	-0.1205	0.3193	0.4742	1.6575	-0.38	0.706
Race (ref=White)							
African American	1.3461	0.2972	0.4441	0.5637	3.2143	0.67	0.5035
Hispanic	2.4210	0.8842	0.5533	0.8186	7.1599	1.6	0.11
Others	1.1096	0.104	0.4806	0.4326	2.8457	0.22	0.8287
Area (ref=Urban)							
Rural	0.8543	-0.1575	0.3662	0.4167	1.7512	-0.43	0.6672
CCI (ref=0)							
1	1.2036	0.1853	0.3984	0.5512	2.6279	0.47	0.6418
2	2.7191	1.0003	0.4296	1.1714	6.3117	2.33	0.0199
≥3	0.4951	-0.703	0.4363	0.2106	1.1642	-1.61	0.1071
Intercept	9366.5490	9.1449	1.1767	933.2751	94014.0953	7.77	<.0001

Note: Exp= Exponentiated

3.7.6 Other visit payments

Based on descriptive analyses, the mean (SD) other visit payment for the overall population was \$340 (\$1,149), with \$358 (\$1,253) for the chemotherapy group, \$348 (\$649) for the immunotherapy group, and \$137 (\$318) for the targeted therapy group. The results from the GLM evaluating other visit payments are shown in Table 3.22. A total of 271 (59.8%) patients had other visit payments. Compared to the chemotherapy group, the immunotherapy group had 42.70% lower other visit payments (exponentiated estimate=0.5730, 95% CI: 0.2826 to 1.1622, $p=0.1227$) with an estimated mean of \$468 (982×0.5730), while the targeted therapy group had 56.54% lower other visit payments (exponentiated estimate=0.4346, 95% CI: 0.2319 to 0.8143, $p=0.0093$) with an estimated mean of \$427 (982×0.4346). Thus, “ H_{05k-l} : There are no significant relationships in the mean lung cancer-related other payments by treatment group, for the immunotherapy (k) and targeted therapy (l) groups compared to the chemotherapy group, while controlling for covariates” was not rejected for H_{05k} (immunotherapy group) but was rejected for H_{05l} (targeted therapy group).

For every one-year increase in age, the other visit payment increased 0.65% (exponentiated estimate=1.0065, 95% CI: 0.9636 to 1.0513, $p=0.7715$). Compared to females, males had 29.86% lower other visit payments (exponentiated estimate=0.7014, 95% CI: 0.4294 to 1.1456, $p=0.1564$) with an estimated mean of \$688 (982×0.7014). Compared to Whites, African Americans had 9.35% lower other visit payments (exponentiated estimate=0.9065, 95% CI: 0.5034 to 1.6322, $p=0.7434$) with an estimated mean of \$890 (982×0.9065); Hispanics had 76.42% higher other visit payments (exponentiated estimate=1.7642, 95% CI: 0.76025 to 4.0943, $p=0.1863$) with an estimated mean of \$1,732 (982×1.7642); and others had 4.10% higher other visit payments (exponentiated estimate=1.0410, 95% CI: 0.5600 to 1.9356, $p=0.8988$) with an estimated mean of \$1,022

(982*1.0410). Compared to patients living in urban areas, patients living in rural areas had 14.45% higher other visit payments (exponentiated estimate=1.1445, 95% CI: 0.6928 to 1.8910, p=0.5981) with an estimated mean of \$1,123 (982*1.1445). Compared to patients without comorbidities, patients with a CCI score of 1 had 48.33% lower other visit payments (exponentiated estimate=0.5167, 95% CI: 0.2446 to 1.0929, p=0.0837) with an estimated mean of \$507 (982*0.5167); patients with a CCI score of 2 had 43.49% lower other visit payments (exponentiated estimate=0.5651, 95% CI: 0.2465 to 1.2959, p=0.1777) with an estimated mean of \$555 (982*0.5651); and patients with a CCI score ≥ 3 had 40.62% lower other visit payments (exponentiated estimate=0.5938, 95% CI: 0.2611 to 1.3503, p=0.2137) with an estimated mean of \$583 (982*0.5938). All results are for treatment group=0 (chemotherapy) and all other covariates=0.

Table 3.22 GLM regression evaluating other visit payments (continuous)

Variables	Exp Estimate	Estimate	Standard Error	95% Confidence Limits		Z	P value
Treatment group (ref=Chemotherapy)							
Immunotherapy	0.5730	-0.5568	0.3608	0.2826	1.1622	-1.54	0.1227
Targeted therapy	0.4346	-0.8333	0.3204	0.2319	0.8143	-2.6	0.0093
Age							
18-63 years old	1.0065	0.0065	0.0222	0.9636	1.0513	0.29	0.7715
Gender (ref=Female)							
Male	0.7014	-0.3547	0.2503	0.4294	1.1456	-1.42	0.1564
Race (ref=White)							
African American	0.9065	-0.0982	0.3001	0.5034	1.6322	-0.33	0.7434
Hispanic	1.7642	0.5677	0.4296	0.7602	4.0943	1.32	0.1863
Others	1.0410	0.0402	0.3164	0.5600	1.9356	0.13	0.8988
Region (ref=urban)							
Rural	1.1445	0.135	0.2562	0.6928	1.8910	0.53	0.5981
CCI (ref=0)							
1	0.5167	-0.6602	0.3817	0.2446	1.0920	-1.73	0.0837
2	0.5651	-0.5707	0.4234	0.2465	1.2959	-1.35	0.1777
≥3	0.5938	-0.5212	0.4191	0.2611	1.3503	-1.24	0.2137
Intercept	981.5177	6.8891	1.1594	101.1597	9522.3791	5.94	<.0001

Note: Exp= Exponentiated

3.7.7 prescription payments

Since only 15 patients had lung cancer-related prescription, GLM is not applicable for this analysis. No conclusions were made for H₀5m-n.

3.7.8 Total payments

Based on descriptive analyses, the mean (SD) total visit payment for the overall population was \$40,320 (\$49,284), with \$34,620 (\$39,550) for the chemotherapy group, \$90,179 (\$79,354) for the immunotherapy group, and \$23,287 (\$35,276) for the targeted therapy group. The results from the GLM evaluating total payments are shown in Table 3.23. Compared to the chemotherapy group, the immunotherapy group had 160.93% higher total payments (exponentiated estimate=2.7093, 95% CI: 2.0838 to 3.5230, $p<0.0001$) with an estimated mean of \$27,984 ($10,329 \times 2.7093$), while the targeted therapy group had 29.99% lower total payments (exponentiated estimate=0.7001, 95% CI: 0.4148 to 1.1815, $p=0.1818$) with an estimated mean of \$7,231 ($10,329 \times 0.7001$). Thus, “H_{05o}-p: There are no significant relationships in the mean lung cancer-related total payments by treatment group, for the immunotherapy (o) and targeted therapy (p) groups compared to the chemotherapy group, while controlling for covariates” was rejected for H_{05o} (immunotherapy group) but not rejected for H_{05p} (targeted therapy group).

For every one-year increase in age, total payments increased 1.78% (exponentiated estimate=1.0178, 95% CI: 0.9962 to 1.0399, $p=0.1066$). Compared to females, males had 14.29% higher total payments (exponentiated estimate=1.1429, 95% CI: 0.9276 to 1.4085, $p=0.2098$) with an estimated mean of \$11,805 ($10,329 \times 1.1429$). Compared to Whites, African Americans had 15.80% lower total payments (exponentiated estimate=0.8420, 95% CI: 0.6478 to 1.0943, $p=0.1983$) with an estimated mean of \$8,697 ($10,329 \times 0.8420$); Hispanics had 46.05% lower total payments (exponentiated estimate=0.5395, 95% CI: 0.3656 to 0.7960, $p=0.0019$) with an estimated mean of \$5,573 ($10,329 \times 0.5395$); and others had 5.38% lower total payments (exponentiated estimate=0.9462, 95% CI: 0.7089 to 1.2630, $p=0.7076$) with an estimated mean of \$9,773 ($10,329 \times 0.9462$). Compared to patients living in urban areas, patients living in rural areas

had 17.29% lower total payments (exponentiated estimate=0.8271, 95% CI: 0.6590 to 1.0382, $p=0.1016$) with an estimated mean of \$8,543 ($10,329 \times 0.8271$). Compared to patients without comorbidities, patients with a CCI score of 1 had 47.98% higher total payments (exponentiated estimate=1.4798, 95% CI: 1.0733 to 2.0405, $p<0.0168$) with an estimated mean of \$15,285 ($10,329 \times 1.4798$); patients with a CCI score of 2 had 55.21% higher total payments (exponentiated estimate=1.5521, 95% CI: 1.0808 to 2.2291, $p=0.0173$) with an estimated mean of \$16,031 ($10,329 \times 1.5521$); and patients with a CCI score ≥ 3 had 54.76% higher total payments (exponentiated estimate=1.5476, 95% CI: 1.0699 to 2.2385, $p=0.0204$) with an estimated mean of \$15,985 ($10,329 \times 1.5476$). All results are for treatment group=0 (chemotherapy) and all other covariates=0.

Table 3.23 GLM regression evaluating total payments (continuous)

Variables	Exp Estimate	Estimate	Standard Error	95% Confidence Limits		Z	P value
Treatment group (ref=Chemotherapy)							
Immunotherapy	2.7093	0.9967	0.1339	2.0838	3.5230	7.44	<.0001
Targeted therapy	0.7001	-0.3566	0.2671	0.4148	1.1815	-1.34	0.1818
Age							
18-63 years old	1.0178	0.0176	0.0109	0.9962	1.0399	1.61	0.1066
Gender (ref=Female)							
Male	1.1429	0.1336	0.1066	0.9276	1.4085	1.25	0.2098
Race (ref=White)							
African American	0.8420	-0.172	0.1337	0.6478	1.0943	-1.29	0.1983
Hispanic	0.5395	-0.6171	0.1985	0.3656	0.7960	-3.11	0.0019
Others	0.9462	-0.0553	0.1473	0.7089	1.2630	-0.38	0.7076
Area (ref=Urban)							
Rural	0.8271	-0.1898	0.116	0.6590	1.0382	-1.64	0.1016
CCI (ref=0)							
1	1.4798	0.3919	0.1639	1.0733	2.0405	2.39	0.0168
2	1.5521	0.4396	0.1847	1.0808	2.2291	2.38	0.0173
≥3	1.5476	0.4367	0.1883	1.0699	2.2385	2.32	0.0204
Intercept	10328.8889	9.2427	0.6579	2844.3789	37503.8923	14.05	<.0001

Note: Exp= Exponentiated

3.8 Summary of hypothesis test results for all objectives

Table 3.24 presents a summary of all results from each hypothesis test for all objectives.

Table 3.24 Results of hypothesis tests

Objectives/hypotheses	Statistical Analysis	Result	Direction
Objective 1. To describe and compare demographic variables (age, gender, race/ethnicity, and urban/rural status) and CCI of the study sample across treatment groups (chemotherapy, targeted therapy, and immunotherapy).			
H ₀ 1a: There are no significant differences in age across treatment groups	Descriptive statistics and ANOVA test	Fail to reject	Immunotherapy group > Chemotherapy group > targeted therapy group but NS
H ₀ 1b: There are no significant differences in gender across treatment groups	Descriptive statistics and chi-square test	Fail to reject	Females dominated in all treatment groups but NS
H ₀ 1c: There are no significant differences in race/ethnicity across treatment groups	Descriptive statistics and chi-square test	Fail to reject	Whites dominated in all treatment groups but NS
H ₀ 1d: There are no significant differences in urban/rural status across treatment groups	Descriptive statistics and chi-square test	Fail to reject	Patients living in urban area dominated in all treatment groups but NS
H ₀ 1d: There are no significant differences in CCI groups across treatment groups	Descriptive statistics and chi-square test	Fail to reject	CCI=0 dominated in all treatment groups but NS
Objective 2. To describe and compare treatment patterns in terms of treatment groups and treatment regimens (e.g., platinum-taxane doublet, platinum-nontaxane doublet, triplet therapy with platinum, single targeted therapy, singlet immunotherapy etc.) by treatment line (first and subsequent treatment).			
H ₀ 2a: There are no significant differences in proportions of patients in treatment groups by treatment line	Descriptive statistics and chi-square test	Reject	Chemotherapy group dominated in first and subsequent line
H ₀ 2b: There are no significant differences in proportions of patients receiving treatment regimens (including chemotherapy regimens, targeted therapy regimens and immunotherapy regimens) by treatment line	Descriptive statistics and chi-square test	Reject	Platinum-based treatments accounted for the majority of first-line treatments, while singlet immunotherapy was the most commonly used treatment in subsequent-line treatment
H ₀ 2c: There are no significant differences in	Descriptive statistics and chi-square test	Reject	Platinum-based treatment was the most frequently

Objectives/hypotheses	Statistical Analysis	Result	Direction
proportions of patients receiving chemotherapy regimens by treatment line			prescribed treatment in first line; while single-agent without cisplatin or carboplatin was prescribed widely in subsequent line
H ₀ 2d: There are no significant differences in proportions of patients receiving targeted therapy regimens by treatment line	Descriptive statistics and Fisher's exact test	Fail to reject	Single targeted therapy was the most frequently prescribed treatment in first and subsequent line but NS
H ₀ 2e: There are no significant differences in proportions of patients receiving immunotherapy regimens by treatment line	Descriptive statistics and chi-square test	Reject	Doublet/triplet immunotherapy was more common in first line, while singlet immunotherapy was prescribed more often in subsequent line
Objective 3. To compare lung cancer-related healthcare utilization among lung cancer patients in terms of hospitalizations, length of hospital stays, ED visits, office visits, hospital outpatient visits, home visits, and other visits by treatment group, while controlling for covariates.			
H ₀ 3a-b: There are no significant differences in the number of lung cancer-related hospitalizations for the immunotherapy (a) and targeted therapy (b) groups compared to the chemotherapy group , while controlling for covariates ^a	Zero-Inflated Negative Binomial models	NS	Model didn't converge
H ₀ 3c-d: There are no significant differences in the number of lung cancer-related length of hospital stays for the immunotherapy (c) and targeted therapy (d) groups compared to the chemotherapy group , while controlling for covariates ^a	Zero-Inflated Negative Binomial models	Fail to reject (c and d)	Immunotherapy group > chemotherapy group but NS; targeted therapy group < chemotherapy group but NS
H ₀ 3e-f: There are no significant differences in the number of lung cancer-related ED visits for the immunotherapy (e) and targeted therapy (f) groups compared to the chemotherapy group , while controlling for covariates ^a	Zero-Inflated Negative Binomial models	Rejected (H ₀ 3e); fail to reject (H ₀ 3f)	Immunotherapy group < chemotherapy group; targeted therapy group < chemotherapy group but NS

Objectives/hypotheses	Statistical Analysis	Result	Direction
H ₀ 3g-h: There are no significant differences in the number of lung cancer-related office visits for the immunotherapy (g) and targeted therapy (h) groups compared to the chemotherapy group , while controlling for covariates ^a	Zero-Inflated Negative Binomial models	Fail to reject (g and h)	Immunotherapy group > chemotherapy group but NS; targeted therapy group < chemotherapy group but NS
H ₀ 3i-j: There are no significant differences in the number of lung cancer-related hospital outpatient visits for the immunotherapy (i) and targeted therapy (j) groups compared to the chemotherapy group , while controlling for covariates ^a	Zero-Inflated Negative Binomial models	Reject	Immunotherapy group < chemotherapy group; targeted therapy group < chemotherapy group
H ₀ 3k-l: There are no significant differences in the number of lung cancer-related home visits for the immunotherapy (k) and targeted therapy (l) groups compared to the chemotherapy group , while controlling for covariates	Zero-Inflated Negative Binomial models	N/A	Model didn't converge
H ₀ 3m-n: There are no significant differences in the number of lung cancer-related other visits for the immunotherapy (m) and targeted therapy (n) groups compared to the chemotherapy group , while controlling for covariates	Zero-Inflated Negative Binomial models	Fail to reject	Immunotherapy group < chemotherapy group but NS; targeted therapy group < chemotherapy group but NS
Objective 4. To compare lung cancer-related payment status (\$0 coded as 0; >\$0 coded as 1) among lung cancer patients in terms of payments for hospitalizations, ED visits, office visits, hospital outpatient visits, home visits, other visits, prescriptions, and total payments by treatment group, while controlling for covariates.			
H ₀ 4a-b: There are no significant relationships between lung cancer-related hospitalization payment status and treatment group , for the immunotherapy (a) and targeted therapy (b) groups	Hurdle model: logistic regression	Fail to reject	Immunotherapy group > chemotherapy group; targeted therapy group < chemotherapy group

Objectives/hypotheses	Statistical Analysis	Result	Direction
compared to the chemotherapy group , while controlling for covariates ^a			
H ₀ 4c-d: There are no significant relationships between lung cancer-related ED visit payment status and treatment group , for the immunotherapy (c) and targeted therapy (d) groups compared to the chemotherapy group , while controlling for covariates ^a	Hurdle model: logistic regression	Fail to reject	Immunotherapy group > chemotherapy group but NS; targeted therapy group > chemotherapy group but NS
H ₀ 4e-f: There are no significant relationships between lung cancer-related office visit payment status and treatment group , for the immunotherapy (e) and targeted therapy (f) groups compared to the chemotherapy group , while controlling for covariates ^a	Hurdle model: logistic regression	Rejected (e); fail to reject (f)	Immunotherapy group > chemotherapy group; targeted therapy group < chemotherapy group but NS
H ₀ 4g-h: There are no significant relationships between lung cancer-related hospital outpatient visit payment status and treatment group , for the immunotherapy (g) and targeted therapy (h) groups compared to the chemotherapy group , while controlling for covariates ^a	Hurdle model: logistic regression	Fail to reject	Immunotherapy group > chemotherapy group but NS; targeted therapy group < chemotherapy group but NS
H ₀ 4i-j: There are no significant relationships between lung cancer-related home visit payment status and treatment group , for the immunotherapy (i) and targeted therapy (j) groups compared to the chemotherapy group , while controlling for covariates ^a	Hurdle model: logistic regression	Fail to reject	Immunotherapy group > chemotherapy group; targeted therapy group < chemotherapy group
H ₀ 4k-l: There are no significant relationships between lung cancer-related other visit payment status and treatment group ,	Hurdle model: logistic regression	Rejected (k); fail to reject (l)	Immunotherapy group > chemotherapy group; targeted therapy group < chemotherapy group but NS

Objectives/hypotheses	Statistical Analysis	Result	Direction
for the immunotherapy (k) and targeted therapy (l) groups compared to the chemotherapy group, while controlling for covariates ^a			
H _{04m-n} : There are no significant relationships between lung cancer-related prescription payment status and treatment group, for the immunotherapy (m) and targeted therapy (n) groups compared to the chemotherapy group, while controlling for covariates ^a	Hurdle model: logistic regression	N/A	Insufficient sample
H _{04o-p} : There are no significant relationships between lung cancer-related total payment status and treatment group, for the immunotherapy (o) and targeted therapy (p) groups compared to the chemotherapy group, while controlling for covariates ^a	Hurdle model: logistic regression	N/A	439 (96.9%) had payments >0
Objective 5. To compare lung cancer-related payments (>\$0; continuous) among lung cancer patients in terms of payments for hospitalizations, ED visits, office visit, hospital outpatient visits, home visits, other visits, prescription and total payments by treatment group, while controlling for covariates.			
H _{05a-b} : There are no significant differences in the mean lung cancer-related hospitalization payments by treatment group, for the immunotherapy (a) and targeted therapy (b) groups compared to the chemotherapy group, while controlling for covariates ^a	Hurdle model: GLM with a gamma distribution and a log link	Fail to reject	Immunotherapy group < chemotherapy group but NS; targeted therapy group < chemotherapy group but NS
H _{05c-d} : There are no significant differences in the mean lung cancer-related ED visit payments by treatment group, for the immunotherapy (c) and targeted therapy (d) groups compared to the	Hurdle model: GLM with a gamma distribution and a log link	Rejected (c); fail to reject (d)	Immunotherapy group < chemotherapy group; targeted therapy group < chemotherapy group but NS

Objectives/hypotheses	Statistical Analysis	Result	Direction
chemotherapy group , while controlling for covariates ^a			
H ₀ 5e-f: There are no significant differences in the mean lung cancer-related office visit payments by treatment group , for the immunotherapy (e) and targeted therapy (f) groups compared to the chemotherapy group , while controlling for covariates ^a	Hurdle model: GLM with a gamma distribution and a log link	Rejected (e); fail to reject (f)	Immunotherapy group > chemotherapy group; targeted therapy group < chemotherapy group but NS
H ₀ 5g-h: There are no significant differences in the mean lung cancer-related hospital outpatient visit payments by treatment group , for the immunotherapy (g) and targeted therapy (h) groups compared to the chemotherapy group , while controlling for covariates	Hurdle model: GLM with a gamma distribution and a log link	Fail to reject	Immunotherapy group > chemotherapy group but NS; targeted therapy group < chemotherapy group but NS
H ₀ 5i-j: There are no significant differences in the mean lung cancer-related home visit payments by treatment group , for the immunotherapy (i) and targeted therapy (j) groups compared to the chemotherapy group , while controlling for covariates ^a	Hurdle model: GLM with a gamma distribution and a log link	Fail to reject	Immunotherapy group < chemotherapy group but NS; targeted therapy group > chemotherapy group but NS
H ₀ 5k-l: There are no significant differences in the mean lung cancer-related other visit payments by treatment group , for the immunotherapy (k) and targeted therapy (l) groups compared to the chemotherapy group , while controlling for covariates ^a	Hurdle model: GLM with a gamma distribution and a log link	Fail to reject (k); rejected (l)	Immunotherapy group < chemotherapy group but NS; targeted therapy group < chemotherapy group
<H ₀ 5m-n: There are no significant differences in the mean lung cancer-related prescription payments by treatment group , for the immunotherapy (m) and	Hurdle model: GLM with a gamma distribution and a log link	N/A	Insufficient sample

Objectives/hypotheses	Statistical Analysis	Result	Direction
targeted therapy (n) groups compared to the chemotherapy group, while controlling for covariates ^a			
H ₀ 50-p: There are no significant differences in the mean lung cancer-related total payments by treatment group , for the immunotherapy (o) and targeted therapy (p) groups compared to the chemotherapy group , while controlling for covariates ^a	Hurdle model: GLM with a gamma distribution and a log link	Rejected (o); fail to reject (p)	Immunotherapy group > chemotherapy group; targeted therapy group < chemotherapy group but NS

a. Covariates include age, gender, race/ethnicity, and urban/rural status.

Chapter 4 Discussion and Conclusions

4.1 Chapter overview

This chapter provides a discussion of the study results. The study purpose is reviewed, followed by comparisons of results to previous studies and possible explanations for the observed findings in order of objectives. Furthermore, limitations and potential implications of this study are discussed.

4.2 Review of study purpose

The first purpose of this study was to update the information regarding lung cancer-related treatments (chemotherapy, targeted therapy, and immunotherapy) used in more recent clinical practice for the Texas Medicaid population. Objective 1 was to describe and compare demographic characteristics and Charlson Comorbidity Index (CCI) scores, and objective 2 was to explore treatment patterns accordingly. The second purpose of this study was to provide information about lung cancer-related healthcare resource utilization and payments on a patient-level basis. Objective 3 evaluated healthcare utilization by treatment groups. Objectives 4 and 5 investigated lung cancer-related payments by treatment group.

4.3 Comparisons with previous studies

4.3.1 Objective 1: Demographic characteristics and clinical characteristics

Objective 1 was to describe and compare demographic characteristics and Charlson Comorbidity Index (CCI) scores of the study sample across treatment groups (chemotherapy, targeted therapy, and immunotherapy).

Of the included 453 enrollees, 364 (80.4%) received chemotherapy, 36 (7.9%) received targeted therapy, and 53 (11.7%) received immunotherapy as the first-line treatment. The mean ages (56.5) were similar across treatment groups with no significant age differences found in the chemotherapy, targeted therapy, and immunotherapy groups. However, our study population was younger than those reported in Medicare-based studies and electronic health record (EHR)-based studies, potentially accounting for differences in study results. [96] [97] [108] [134] [146] [106] [147] [148] [93] [149] [150]

The proportion of females was slightly higher than males overall and that pattern was consistent across the treatment groups and with recent studies which found more women than men with lung cancer. [151] [152] Although the incidence rates of lung cancer have steadily decreased in the US in recent years, the incidence rate in women decreased at one-half the pace of that in men from 2015 through 2019, leading to greater female-to-male incidence rate ratios. [153] Whites and Blacks accounted for a majority of the study population, which is consistent with previous studies. [19, 20] Enrollees with lung cancer from urban areas made up approximately two-thirds of the study population which is consistent with composition of overall Texas Medicaid enrollment.

Regarding CCI scores, most lung cancer patients had comorbidities (77.5%) with 40.4% of enrollees having a CCI score of 1, 22.1% of enrollees having a CCI score of 2, and 15% of enrollees having a CCI score of 3 or more. Chronic pulmonary disease (40.4%) was the most common comorbidity, followed by myocardial infarction (21.4%), and diabetes with and without complications (20.3%). Chronic obstructive pulmonary disease (COPD) and lung cancer share pathological mechanisms and people with COPD have a greater risk of developing lung cancer. [154] [155] [156] [157] The association of diabetes, heart disease and lung cancer was also well

documented in previous studies. [158] [157] [159] Previous studies showed that comorbidities may impact treatment options and treatment outcomes. [159] [160]

4.3.2 Objective 2: Treatment patterns

Before 2015, platinum-based chemotherapy was the standard of care for metastatic/advanced NSCLC. However, the treatment landscape has changed with approval of new treatments in recent years. Objective 2 was to describe and compare treatment patterns in terms of treatment groups and treatment regimens by treatment line (initial and subsequent treatment).

4.3.2.1 Treatment Groups by Treatment Line

In our study, chemotherapy was the most frequently prescribed first- and second-line treatment for enrollees with lung cancer, which was consistent with NCCN recommendations and previous studies. [108] [134] [146] We observed the proportion of patients receiving chemotherapy in first line (80.1%) was much higher than those receiving chemotherapy in subsequent line (46.2%). Meanwhile, the use of immunotherapy increased in subsequent-line treatment. Nearly equal proportions of patients received immunotherapy and chemotherapy in subsequent-line treatment, indicating treatment paradigm shifts from chemotherapy to immunotherapy. In a retrospective analysis of patients with advanced NSCLC, Nadler et al. also found that the most common treatment sequences were first-line systemic chemotherapy to second-line immunotherapy. [134] It is likely that many patients who received chemotherapy in the first-line treatment couldn't tolerate the toxicity of chemotherapy, or their condition progressed on first-line therapy and they opted for immunotherapy in subsequent-line treatment. This pattern reflects the adoption of immunotherapy in subsequent-line treatment.

Compared to the high proportion of immunotherapy used in subsequent line, only 11.7% of patients received immunotherapy in first-line treatment. Such a result is generally consistent with the sequence of FDA approval of immunotherapy. The US FDA granted approval for pembrolizumab and nivolumab to treat patients with advanced/metastatic NSCLC whose disease has progressed after other treatments in 2015. Pembrolizumab was the first immunotherapy approved by the US FDA for first-line treatment of NSCLC patients with tumor cell PD-L1 expression $\geq 50\%$ (October 2016). As the evidence continued to accumulate, the FDA successively granted approval for atezolizumab in combination with platinum-based chemotherapy and bevacizumab for first-line treatment of metastatic non-squamous NSCLC, pembrolizumab in combination with chemotherapy for first-line treatment of metastatic squamous NSCLC (October, 2018), and pembrolizumab in combination with chemotherapy for first-line treatment of metastatic non-squamous NSCLC (April, 2019), regardless of the PD-L1 expression level. Increasing uptake of immunotherapy (atezolizumab, nivolumab, and pembrolizumab) was seen in prior studies after respective approvals. [134] [148] [147] Given the recent approval of immunotherapy in non-squamous NSCLC, as well as extended indications to lower tumor PD-L1 expression levels in first-line treatment, immunotherapy was used more in subsequent line; however, it shifted toward earlier lines. Nadler et al. showed that the proportion of patients receiving first-line immunotherapy increased from 2.1% in the second quarter of 2015 to 36.0% in the second quarter of 2018 in the U.S. community oncology setting. [134] Using same database (Flatiron Health Oncology), Stenehjem et al. found that only 20% of patients received chemotherapy as first-line treatment while 75% of patients received immunotherapy during August 2018 and December 2019, which indicated a widespread use of immunotherapy after its approval. [148] However, our study did not analyze treatment patterns across years. It would be meaningful

to explore whether there is increased adoption of immunotherapies over a broader time period in future research.

The use of targeted therapy is limited with a slight increase in subsequent line (first line: 8.2% and subsequent line: 10.9%). Similarly, Nadler et al. found that targeted therapy was used in only 8.5% of patients in first-line treatment and more patients (37%) received targeted therapy in second-line treatment. [134] However, the rate of targeted therapy was relatively high (19%) as reported in a study by Spence et al. due to a different study period and population. [106] Fewer patients receiving targeted therapy may be because targeted therapy was recommended for specific groups of patients only. For example, the NCCN guidelines recommend erlotinib, gefitinib, or afatinib for patients with metastatic non-squamous NSCLC who are EGFR positive, regardless of their performance status. Crizotinib is recommended for patients who are positive for the ALK gene rearrangement. [5]

In summary, our study showed that although use of immunotherapy increased especially in subsequent line, chemotherapy remained the cornerstone treatment option for patients with lung cancer. Our findings are consistent with published studies that have evaluated treatment patterns after approval of immunotherapy. [134] [148] [147] The results indicate that immunotherapy is becoming more common place in the treatment of NSCLC.

4.3.2.2 Treatment regimen by treatment line

Chemotherapy

Traditionally, chemotherapy is the standard of care for lung cancer patients. Consistent with previous studies and NCCN guidelines, we found that platinum-based doublets were the main

first-line treatment while single-agent chemotherapy dominated in subsequent line. In our study, carboplatin-based doublets were frequently used in first line. The most common chemotherapy received in first line was a combination of carboplatin and paclitaxel (33.9%), and platinum-based nontaxane regimens accounted for a third of first-line treatment (carboplatin-etoposide: 14.3%; cisplatin-etoposide: 13.8%; carboplatin-pemetrexed: 9.6%). In second line, although carboplatin-paclitaxel was still the most commonly used chemotherapy, singlet-agent chemotherapy was frequently used (paclitaxel: 17.6%; pemetrexed: 14.1%; carboplatin/cisplatin: 9.4%; docetaxel: 4.7%; gemcitabine: 4.7%).

A series of Medicare-based studies showed the same treatment patterns. [93] [96] [97] [161] Lang et al. assessed first-line chemotherapy treatment patterns and reported that doublet chemotherapy was used in 74% of Medicare enrollees, ranging from 67% among those diagnosed in 1999 to 77% among those diagnosed 2001. [93] Platinum plus a taxane (docetaxel/paclitaxel) were the most frequently used first-line chemotherapy regimens across study years (53.7%). In a similar study time period, Davidoff et al. reported that two-thirds of Medicare enrollees received a platinum-doublet regimen in first line and more than half of enrollees received a single agent during in second line 1997 and 2002. [96] In another study by Davis et al., platinum-based doublets were the most common first-line chemotherapy with carboplatin-based doublets most frequently used (carboplatin plus paclitaxel: 45.74%; carboplatin plus gemcitabine: 10.12%; and carboplatin plus docetaxel: 9.32%). [97] A wide range of single agents were used in second and third lines from 2001 to 2010 (gemcitabine: 16.15%; docetaxel: 13.48%; pemetrexed: 11.04%; vinorelbine: 6.08%; paclitaxel: 6.05%; and carboplatin: 3.47%). A recent Medicare-based study summarized use patterns of adjuvant chemotherapy in patients with early-stage NSCLC from 2007 to 2019. [161] More than 90% of patients received platinum-based doublets including 55.7% receiving a

carboplatin-based regimen and 42.8% receiving a cisplatin-based regimen. The most frequently used platinum-based adjuvant chemotherapy was carboplatin-paclitaxel (24.5%), followed by cisplatin-vinorelbine (15.2%), carboplatin-pemetrexed (14.8%), and cisplatin-pemetrexed (13.4%), with only a few patients receiving single-agent treatment.

The same treatment pattern was not only observed in Medicare enrollees, but also found in a wider population with recent data. Abernethy et al. evaluated first-line treatments prescribed among NSCLC patients without EGFR mutations or ALK rearrangements in the US community oncology setting before the introduction of immunotherapy (2012-2015). [162] [163] [164] Overall, carboplatin doublets were prescribed to approximately half of patients, while cisplatin doublets were prescribed to only 4% of patients with various regimens used. Regimens prescribed to >10% of all patients included carboplatin-pemetrexed (20.3%), carboplatin-paclitaxel (19.1%), and carboplatin-bevacizumab-pemetrexed (12.5%). In another retrospective study examining treatment patterns in patients with unresected stage IIIA and IIIB NSCLC from 2011 to 2016, a regimen with platinum plus a taxane without radiation was identified in the majority of patients in the first progression interval and non-platinum single chemotherapy was the most common treatment in the second and third progression intervals. [163] Simeone et al. further analyzed treatment patterns from 2013 and 2017. [164] Carboplatin-paclitaxel (18.6%) was the most common first-line therapy, followed by carboplatin-pemetrexed (16.6%) and carboplatin-pemetrexed-bevacizumab (11.3%). After FDA approval for second-line treatment, immunotherapy and targeted therapy were shown in subsequent line. However, singlet chemotherapies, including pemetrexed, docetaxel, gemcitabine, and vinorelbine were frequently prescribed.

Overall, previous studies have consistently shown that platinum-based doublets were the most common chemotherapy regimens in first line. Carboplatin plus paclitaxel or pemetrexed comprised the most common first-line chemotherapy regimen. Subsequent-line treatments were varied but singlet chemotherapy accounted for the most. These studies were based on Medicare data preceding the advent of targeted and immunotherapy, as well as EHR oncology databases from 2011 to 2017. Our study results confirmed this pattern using a broader study time period, which indicates the treatment patterns of chemotherapy are not changing even with approval of new therapy.

4.3.2.3 Targeted therapy

With regard to targeted therapy, we observed that the use of single targeted therapy and doublet/triplet targeted therapy were equally distributed in first- and subsequent-line treatments. Bevacizumab, as singlet therapy (first line: 32.4%, subsequent line: 25%) or combined with chemotherapy (first line: 35.1%, subsequent line: 40%), was the most common targeted regimen. EGFR TKIs were used less in this study. In first-line treatment, the most common TKI was osimertinib (10.8%). Only 5.4% of patients received dacomitinib. First-generation (erlotinib and gefitinib) and second-generation (afatinib) TKIs were used in only 16.3% of patients. In second-line treatment, osimertinib accounted for 20% and the first- and second-generation TKIs accounted for 15%.

The wide use of bevacizumab could be explained by earlier approval for advanced NSCLC and approvals for a number of biosimilars. The FDA approved Avastin (bevacizumab) to be used in combination with carboplatin and paclitaxel chemotherapy for first-line treatment of patients

with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer (NSCLC) in 2006. [165] Bevacizumab biosimilars include Mvasi (Amgen and Allergan, 2017), Zirabev (Pfizer, 2019) and Almysys (mAbxience, 2022). [166] [167] [168] [169] In contrast, the first-generation EGFR TKIs (erlotinib and gefinib) were approved for first-line treatment of EGFRm patients in 2013 and 2015, respectively. The second-generation EGFR TKIs (afatinib and dacomitinib) received FDA approval for first-line treatment of EGFRm patients in 2018. Additionally, bevacizumab is a type of targeted therapy drug called a monoclonal antibody. It works by attaching to a protein called VEGF, which makes blood vessels grow. Unlike TKIs, bevacizumab could be used in a more general population.

Real-world analyses of treatment patterns with targeted therapy are limited. [162] [170] [108] Abernethy et al. showed that among NSCLC patients without EGFR mutations or ALK rearrangements, 23% were treated with a carboplatin doublet plus bevacizumab, consisting of 1% squamous NSCLC patients and 29% non-squamous NSCLC patients in first-line treatment from 2012 to 2015. [162] Among NSCLC in general, bevacizumab with paclitaxel and carboplatin (13%) was shown as one of the most frequently used first-line treatments. [108] TKIs accounted for only 6% in first-line treatment with 3.7% and 0.8% of patients receiving erlotinib and crizotinib, respectively. Higher use of TKIs (17%) was observed in second line with erlotinib used most frequently (11%). Using regional data (Kaiser Permanente California), Spence et al. found that less than 10% of patients received bevacizumab and more patients (19%) received TKIs between 2008 and 2013. [106] The results in previous studies regarding treatment patterns of targeted therapy were inconsistent given different study populations and study designs. The use of bevacizumab was relatively high in our study most likely due to the longer and more recent study period.

A number of studies addressed the use of TKIs only. [170] [149] [150] Using the IQVIA database, Shenolikar et al. showed that first-generation EGFR TKIs (erlotinib and gefitinib) accounted for most first-line treatments from 2015 to 2017 (60.6%-80.9%) and second-generation EGFR TKIs (afatinib and dacomitinib) accounted for 18.6%-29.6% of first-line EGFR TKIs. [170] A third-generation EGFR TKI (osimertinib) was becoming the most common first-line EGFR TKI after 2018, the year it received FDA approval. In another retrospective study using MarketScan® Commercial and Medicare Supplemental Databases, the most frequently prescribed first-line EGFR TKI was erlotinib (72%), followed by afatinib (26%), and gefitinib (3%). [150] Additionally, 3% of patients received TKIs in combination with bevacizumab. The most frequently received second-line treatment was osimertinib (46%). With documented EGFR mutation, patients with advanced NSCLC in the Flatiron HER database were widely treated with EGFR TKIs as first-line treatment between 2011 and 2017. [149] Over half of patients received erlotinib (61.7%), followed by afatinib (9.1%), and gefitinib (1.4%). Erlotinib (32.7%) was also most common second-line treatment. Osimertinib was not included in this study.

It was not possible to capture biomarker status as the Medicaid database lacked comprehensive and structured biomarker information. This may explain the low rate of TKI use in this study. In general, EGFR mutations account for up to 24% of NSCLC cases in the US. It was not possible to know whether the prevalence of EGFR mutation in this study was lower than that in previous studies. On the other hand, the FDA limited erlotinib to the treatment of metastatic NSCLC patients with EGFR mutations in October 2016. Our results reflect constrained use of erlotinib. The proportion of patients receiving targeted therapy varied among the studies depending on how the study population was selected and what treatments were included. However, our study

confirmed that use of osimertinib exceeds that of first- and second-generation TKIs, becoming widely used in patients with NSCLC.

4.3.2.4 Immunotherapy

In our study, we found there is a significant difference in proportions of patients receiving immunotherapy regimens by treatment line. Doublet/triplet immunotherapy was more common in first line, while singlet immunotherapy was prescribed more often in subsequent line. This pattern follows the NCCN guidelines of immunotherapy treatment for advanced NSCLC. In our study, carboplatin-based immunotherapy was the most common combination immunotherapy in first-line treatment with carboplatin-pemetrexed-pembrolizumab accounting for nearly 40%. Although single immunotherapy was approved only for second-line treatment, we found pembrolizumab (24.5%) and nivolumab (9.4%) were commonly used in first line, indicating adoption of immunotherapy use in frontline treatment. The increasing trend of first-line immune-monotherapy was seen in real-world practice. [134]

In subsequent-line treatment, we observed that nivolumab was initiated in nearly 38% of patients. Durvalumab and pembrolizumab each accounted for about 20% of patients. The higher proportion of nivolumab than pembrolizumab in subsequent line is likely related to required PD-L1 testing for pembrolizumab. The most commonly received immunotherapy plus chemotherapy regimens were pemetrexed-pembrolizumab (6.3%), carboplatin-paclitaxel-pembrolizumab (2.5%), and carboplatin-etoposide-atezolizumab (2.5%).

Three recently published studies evaluated treatment patterns of immunotherapy in patients with advanced NSCLC using data from the Flatiron Health EHR database. [148] [146] [147] Simeone et al. found that nivolumab was the most commonly prescribed second- and third-line

therapy between 2013 to 2017. [146] This result indicated that nivolumab was used off-label before its approval. The study reported the top five treatments by treatment lines, but no immunotherapy was seen in first-line treatment, which could be explained by a short follow-up time since immunotherapy was approved for first-line treatment for advanced NSCLC (2016). In more recent years (2018 to 2020), Stenehjem et al. showed that patients became more likely to receive immunotherapy. Pembrolizumab-containing treatments accounted for 72% among patients receiving immunotherapy plus chemotherapy in first line. [148] The most commonly prescribed immunotherapy plus chemotherapy regimens were pembrolizumab + carboplatin + pemetrexed (67%), pembrolizumab + carboplatin + paclitaxel (13%), and pembrolizumab + carboplatin + nab-paclitaxel (10%). Among patients who received second-line treatment, immunotherapy plus chemotherapy and immune-monotherapy were equally distributed. Pembrolizumab combination accounted for 25%, followed by pembrolizumab (2.93%), nivolumab (2.73%), and durvalumab (1.13%). Another study showed a general trend of increasing use of immunotherapy and shifting toward earlier line during the early adoption period after the initial approval in advanced NSCLC. [147]

In summary, immunotherapy was usually prescribed with chemotherapy as first-line treatment and used alone as subsequent-line treatment. Pembrolizumab plus carboplatin-based chemotherapy regimens were frequently used as previously noted. Immune-monotherapy (pembrolizumab and nivolumab) was used as first-line treatment, which suggests that immunotherapy is being used more frequently as a preferred treatment option.

4.3.3 Objective 3: Healthcare utilization

Chemotherapy and immunotherapy are usually administered via infusion, while targeted therapy is usually administered orally, except for bevacizumab. Additionally, chemotherapy is usually given for a fixed number of cycles, whereas patients could take immunotherapy or targeted therapy until disease progresses. The differences in route or duration of treatment may have an impact on healthcare utilization. Objective 3 was to assess lung cancer-related healthcare utilization (measured as hospitalizations, length of hospital days, ED visits, office visits, hospital outpatient visits, home visits, and other visits) by treatment group.

4.3.3.1 Hospitalization

Inferential comparisons of hospitalizations for the immunotherapy and targeted therapy groups with those of the chemotherapy group were not feasible since the regression model did not converge (likely due to the relatively small group of patients (165 patients, 36.4%) who experienced hospitalizations). Our results focused on descriptive analyses. Previous studies, using data from Medicare, cancer registries, or the HealthCore Integrated Research Database, reported that the average number of hospitalizations ranged from 1.9 to 2.7. [97] [171] [172] Our study results, which ranged from 2.0 to 2.4, were consistent with those studies. Previous studies have shown that healthcare resource utilization was driven by hospitalization due to adverse event (AE) management. [173] [174] This may explain the low rate of hospitalizations seen in this study since we only included lung cancer-related hospitalizations but not those due to AE management. Dr. Kenny Nguyen, an oncology pharmacist at Texas Oncology, noted in an email exchange that most treatments for lung cancer are administered in the outpatient clinic setting when patients are stabilized, which may also be a factor contributing to the low rate of hospitalization seen in our data. [175]

4.3.3.2 Length of hospital stays

Findings on length of hospital stays in previous studies varied widely due to different data sources and study designs. The longest length of stay was seen in a recently published retrospective study using data from the HealthCore Integrated Research Database (HIRD). [172] Patients with advanced or metastatic NSCLC in the United States between 2010 and 2019 had a mean length of stay per patient per year (PPPY) of 33.4 days during the entire follow-up period. However, PPPY should be interpreted with caution since many patients in this analysis had less than 1 year of follow-up, and the resulting hospitalization length of stay was numerically expanded. In another retrospective study using the Vector Oncology Data Warehouse, which contains electronic medical records and billing data collected at a network of community oncology practices mainly in the Southern and Midwestern US between 2007 and 2014, patients experienced 6.16 (6.28) days of hospital stay during adjuvant treatment and 6.14 (5.93) days for the period from diagnosis to the end of the first regimen after disease recurrence or end of the study. [176] Given the study period, no targeted therapy or immunotherapy were used during adjuvant treatment and only about 28% of patients received targeted therapy (bevacizumab and erlotinib) after disease recurrence. Using a shorter study period and data from a regional cancer registry, a study by Bradley et al. showed that individuals with advanced NSCLC experienced 4 days of hospital stay during one year after diagnosis in California (2009-2012). [177] While another study by Michael et al. showed that the median length of stay for chemotherapy-related hospitalization was 5 days in Northeastern Massachusetts (2003-2006). [178] All of these studies only reported descriptive results; no comparisons in length of stay by treatment group were made.

Our study found that the expected lengths of stay for the immunotherapy and targeted therapy groups were similar to the chemotherapy group. A previous study compared healthcare

utilization among Veterans receiving second-line immunotherapy or chemotherapy (2012-2017). That study reported that the mean length of stay was numerically lower for chemotherapy patients than for immunotherapy patients (9.1 ± 2.9 vs. 9.9 ± 2.9), but no significant difference was found. [179]

4.3.3.3 ED Visits

Unplanned hospital care (e.g., ED visits) is an important marker of poor outcomes. In a study using California Cancer Registry data, Whitney et al. found that patients with lung cancer had a significantly higher rate of ED visits than those with other cancers except for hepatobiliary and pancreatic cancer. [180] A large proportion (86.1%) of patients had ED visits in our study, which is consistent with previous studies. [171] [97] Shah et al. found that the leading cause of ED visits was NSCLC itself, contributing to 61% of ED visits in the TKI therapy group, 49% in the immunotherapy group, and 42% in the chemotherapy group. The study also assessed ED visits attributable to TKI therapy, immunotherapy, and chemotherapy. TKI therapy and immunotherapy appeared to be less likely than chemotherapy to lead to unplanned ED visits (2% vs. 12% vs. 21%).

Our study found the mean number of ED visits was 4.5 for the overall population, which was similar to that reported in a real-world retrospective study using SEER Medicare data. [97] However, that study only included chemotherapy given that no targeted therapy and immunotherapy were approved during the study period. With more recent data, Zhang et al. reported that the mean (SD) number of ED visits PPPY was 1.2 using the HealthCore Integrated Research Database (HIRD). Compared to our study which focused on Texas Medicaid patients, Zhang et al.'s study population was more representative of the US population covered by commercial insurance (78.3%) and Medicare (21.7%).

We found the estimated number of ED visits was significantly lower in patients receiving immunotherapy than chemotherapy. A prior study, including data from traditional fee-for-service commercial plans, Medicare Advantage, managed Medicare, Medicaid, and dual-eligible plans, showed a lower rate of ED visits among patients receiving systematic anticancer treatment in the post-immunotherapy period compared to pre-immunotherapy period. [181] This study supported our result that immunotherapy is associated with lower ED visits. However, in a retrospective study using reimbursed administrative claims data from the IBM Watson Health MarketScan Commercial and Medicare Supplemental Claims and Encounters databases (2020), mean per-patient ED visits per six months was significantly higher among immunotherapy-treated versus non-immunotherapy-treated patients (0.9 vs. 0.8; $p=0.0001$). [182] It should be noted that patients receiving chemotherapy and targeted therapy were combined in the non-immunotherapy-treated cohort; therefore, identification of which treatment contributed to the result is not possible.

We found that targeted therapy was also associated with fewer ED visits, although the relationship was not significant. No similar study comparing targeted therapy and chemotherapy was found; however, a study by Vanderpoel et al. described healthcare utilization among patients receiving osimertinib as first-line treatment using IBM MarketScan Research Databases. [183] ED visits were observed for 39.7% of the osimertinib subgroup and 31.1% of the chemotherapy subgroup. The mean per-patient-per month number of days with ED visits was 0.14 days for the osimertinib subgroup, and 0.18 days for the chemotherapy subgroup. The study results indicated that patients receiving targeted therapy had fewer ED visits.

4.3.3.4 Office visits

Physician office visits are an important way to access ambulatory care. A study using the 2001-2003 National Ambulatory Medical Care Survey (NAMCS) and the National Hospital

Ambulatory Medical Care Survey (NHAMCS) showed that a majority of cancer patients (87%) visited physician offices, with the remainder visiting hospital clinics. [184] Similar to that study, our study found that 77.3% of patients had lung-cancer related office visits. On average, each patient had more than one office visit per month during the 1-year follow-up period (19.8 visits per year), with more use in the immunotherapy group (21.8) and less use in the targeted therapy group (12.8). Two previous studies also showed a high level of physician office visits. [172] [176] Zhang et al. found that the mean number of office visits PPPY was 32.2, which was the second highest factor contributing to healthcare utilization. [172] Bucks et al. reported that almost all patients (99%) receiving care in community-based clinical practice had office visits during the period 2007 to 2014. [176] The average number of office visits was 11.34, which was higher than hospitalizations (0.25). It should be noted that no immunotherapy was included in that study; only erlotinib was included in the study and the frequency of office visits was lower than our study results. The results of the noted studies indicated that most lung cancer-related follow-up visits occurred in physician offices. Thus, understanding characteristics of office visits is important to improve treatment outcomes.

Our study found that patients receiving immunotherapy were slightly more likely to receive treatment in physicians' offices compared to those receiving chemotherapy, although the relationship was not significant. The higher level of office visits associated with immunotherapy has similarly been observed previously. [182] [179] Nesline et al. reported that the mean number of all-cause office visits were significantly higher in the immunotherapy group as compared to the non-immunotherapy group (3.7 vs. 3.2, $p < 0.0001$). [182] Williams et al. also found using bivariate analyses that patients receiving second-line immunotherapy had significantly more oncology

outpatient visits (14 vs. 9, $p < 0.0001$). [179] However, analysis of these variables using logistic and mixed linear regression showed no significant differences.

The relatively high utilization in office visits among patients receiving immunotherapy could be due to several reasons. First, it is safer and more manageable compared to chemotherapy. Immunotherapy has fewer severe adverse events requiring monitoring or intervention in a hospital. Second, patient experience during physician office visits is also an important factor for choosing it. As shown in a previous study, patients visiting oncologists also tend to have a higher level of satisfaction and perceived quality, as well as more be likely to receive anticancer therapy. [185] Our study found that office visits for patients receiving targeted therapy were similar to those receiving chemotherapy. However, no previous studies comparing targeted therapy to chemotherapy with respect to office visits were identified.

4.3.3.5 Hospital outpatient visits

A study by Richardson et al. showed that younger patients (45-64 years of age) or patients covered by Medicaid were shown to present at greater proportion in hospital outpatient clinics than in office practice. [184] Previous studies showed that healthcare utilization was driven primarily by outpatient visits. [172] [97] [183] In the previously mentioned Medicare-based study by Davis et al., 88% of patients had at least one NSCLC-related outpatient visit with an average of 10.5 visits during follow-up. [97] Vanderpoel et al. reported that over 99% of patients receiving targeted therapy or chemotherapy as first-line treatment had an outpatient visit. The mean PPPM for outpatient visits was much higher than for other healthcare resource utilization. [183] Our study found that nearly 80% of Medicaid enrollees visited hospital outpatient clinics, also indicating that patients frequently visited hospital outpatient settings for follow-up care. However, the average number of hospital outpatient visits was lower than office visits in this study.

Because academic health centers and large urban hospitals have limited resources and tend to serve larger proportions of people who are uninsured, covered by Medicaid, or low-income populations, they may provide less expensive treatments, such as chemotherapy, for cancer patients. Our study found patients receiving immunotherapy were about 30% less likely to visit hospital outpatient clinics, although the relationship was not significant. Contrary to our findings, Nesline et al. showed that semiannual outpatient visits were significantly higher in immunotherapy-treated patients compared to non-immunotherapy treated patients (14.4 vs. 11.7, $p < 0.0001$). [182] The non-immunotherapy treated cohort consisted of chemotherapy and targeted therapy in this study, and thus the results were not comparable. In addition, patients receiving targeted therapy were significantly less likely to visit hospital outpatient clinics in our study. However, we didn't find previous studies comparing utilization of targeted therapy to chemotherapy with respect to hospital outpatient visits.

4.3.3.6 Other visits

Other visits consist of many different types of healthcare facility visits in this study, such as laboratory visits, hospice admission, nursing facility admissions, and others. We found patients receiving immunotherapy or targeted therapy were less likely to have other visits compared to those receiving chemotherapy; however, the relationships were not significant. Previous studies reported different indicators (e.g., proportion of patients, number of days, and number of visits). Using Medicare data (2001-2009), Davis et al. reported that approximately half (47%) of patients initiating a cancer-directed treatment had at least one NSCLC-related hospice admission, 18% had at least one NSCLC-related skilled nursing facility admission, and half had at least one NSCLC-related other ancillary care visit. [97] Similar to that study, we found over half of patients (55.8%) had other visits, indicating it is an important way for patients to receive examinations, treatment,

and other health care during follow-up. Using data from HIRD (2010-2019), Zhang et al. reported that the mean number of laboratory encounters was 2.9 PPPY during follow-up, which was lower than outpatient visits and office visits. [172] Only one study compared other services use across treatments. The study showed that number of days with other services was lower in the targeted therapy group compared to the chemotherapy group. [183]

4.3.4 Objective 4&5: Healthcare payments

Given the transformation in the treatment landscape of lung cancer, the economic burden of lung cancer may have changed. Although costs of targeted therapy and immunotherapy are higher than chemotherapy, increased treatment costs may be offset by lower healthcare resource use including hospitalizations and emergency department visits because immunotherapy and targeted therapy are associated with better safety profiles and survival outcomes. [186] [187] The results for objectives 4 and 5 will be discussed in this section since they both compare lung cancer-related payments among lung cancer patients in terms of payments for hospitalizations, ED visits, office visit, hospital outpatient visits, home visits, other visits, prescription, and total payments by treatment group, while controlling for covariates. The discussion of these results focuses on comparisons among treatment groups; the results for covariates are not discussed.

Through the literature review, we found that previous studies evaluating lung cancer-related payments were limited and most of them employed descriptive analyses only. Additionally, studies usually reported overall costs including different components. Thus, the study results between those studies and our study are not directly comparable.

4.3.4.1 Hospitalization payments

Hospitalization costs were reported as the major driver of lung cancer-related costs in studies by Davis et al. and Iadeluca et al. [97] [188] However, targeted therapy and immunotherapy were not included in these studies which included patients diagnosed with lung cancer before 2015. [97] [188] The first real-world study (2018) evaluating healthcare costs in patients with advanced NSCLC who initiated targeted therapy as first-line or second-line therapy and experienced disease progression, which was conducted by Skinner et al., also demonstrated that hospitalization costs represented the greatest proportion of the total mean monthly cost. [128] Close to half of the total mean monthly cost was attributed to hospitalizations (47.0%; \$9,454 [95% CI: \$6,551–\$12,358]). The mean monthly cost of hospitalization in the post-disease progression period was higher in patients who received systemic anti-cancer therapy than in those who did not (\$20,490 [95% CI: \$16,111–\$24,870] vs \$15,364 [\$6,384–\$24,344]; $p < 0.001$). In recent studies, hospitalization costs were still high, but they accounted for a lower percentage of total costs. [172] [182] A study by Zhang et al. (2022) reported that mean inpatient cost paid by both payers and patients was \$72,132 PPPY during the entire study follow-up, accounting for 29% of total costs. [172] Our study found that mean hospitalization payments accounted for only 12% of total payments in the overall population, 14% in chemotherapy group, 8% in immunotherapy group, and 5% in targeted therapy group.

Another study by Nesline et al. reported that semi-annual hospitalization costs paid by payers in 2017 were significantly higher in patients receiving immunotherapy compared to those receiving chemotherapy and targeted therapy (\$18,701 vs. \$18,389, $p = 0.0004$). [182] Hospitalization costs accounted for only 13% of total costs in immunotherapy-treated patients. Our study found that hospitalization payments for the immunotherapy group accounted for less than

10% of total payments, although the mean hospitalization payment for the immunotherapy group was high (\$7,034) during the 1-year follow-up. Additionally, a study by Vanderpoel et al. (2023) described healthcare costs paid by payers among patients initiating with osimertinib or chemotherapy. [183] Hospitalization costs PPPM for the osimertinib group were higher ($\$5,462 \pm 27,961$ vs. $\$1,166 \pm 3,203$). In contrast, we found that the mean hospitalization payment for targeted therapy was lower than for chemotherapy ($\$1,363$ vs. $\$4,794$). However, since only 37 patients received targeted therapy in our study and even fewer incurred hospital expenses, the mean payments were likely underestimated.

Using a hurdle model, we found that patients receiving immunotherapy were associated with lower hospitalization payments compared to those receiving chemotherapy, although patients receiving immunotherapy were more likely to have a hospitalization payment. Hospitalization payments for the targeted therapy group were lower compared to the chemotherapy group. Considering the similar lengths of stay for the immunotherapy, targeted therapy, and chemotherapy groups (see discussion of objective 3), the study results indicated that patients receiving immunotherapy or targeted therapy may have experienced fewer adverse events and achieved better treatment outcomes during hospitalization, resulting in lower payments.

4.3.4.2 ED visit payments

In the previously mentioned Medicare-based study by Davis et al., the mean (SD) NSCLC-related ED visit cost was \$366 (\$378) for patients with NSCLC diagnosed between 2001 and 2009, which was much lower than for other types of healthcare costs. [97] Findings from our study also showed that ED visit costs were consistently low, even considering patients receiving immunotherapy or targeted therapy. We further found that the immunotherapy and targeted therapy groups were associated with lower ED visit payments. In contrast, a previous study by

Nesline et al. found that the mean semiannual payments for ED visits were higher in the immunotherapy group compared to the non-immunotherapy group (\$1,096 vs. \$864). [182] The opposite results may explained by their study assessing higher reimbursements by commercial health insurance during 2015 and 2017, while our study employed Texas Medicaid data.

4.3.4.3 Office visit payments

As discussed in objective 3, healthcare resource utilization was driven primarily by office visits. Consequently, office visit payments constituted of the largest proportion of total costs. A study by Iadeluca et al. found that Medicare spending was driven by inpatient hospital and office-based visits, which accounted for 38.6% and 28.5% of total Medicare spending, respectively. [188] Our study differed from that study in that inpatient hospital costs only represented 12% of total payments in the overall population.

The mean office visit payments were highest for the immunotherapy group (\$64,410), followed by the chemotherapy group (\$17,433), and the targeted therapy group (\$16,052). We also found that the immunotherapy group had 218.96% higher office visit payments; while the targeted therapy group had 6.39% lower office visit payments, controlling for the covariates. A previous study by Nesline et al. showed similar patterns in payments for office visits. [182] They reported that mean semiannual costs of specialist office visits in immunotherapy-treated patients were 3 times higher than in patients without immunotherapy. [182] Primary care physician office visit costs in the immunotherapy cohort were more than 6-fold higher compared to non-immunotherapy cohort. Contrary to our study results, a retrospective study by Haslem et al. reported office visit payment for patients receiving targeted therapy were 71.1% higher than those receiving standard treatment (\$6,265 vs. \$ 3,663). [186] However, their study included a small number of patients (44) from the institutional enterprise.

However, the high office visit payments seen in our study may be mainly attributed to drug payments rather than service payments. Physician office visit costs were only \$160 per month in a study assessing Medicare-paid costs by Skinner et al. [128] Similarly, another study by Buck et al. also reported that office visit costs were only \$105.45 while chemotherapy or targeted therapy costs were \$1,030.60 and \$2,275.25, respectively. [176]

4.3.4.4 Hospital outpatient payments

Hospital outpatient payments, instead of hospital inpatient payments, were a key driver of total health payments in recent studies. [182] [172] Similarly, we found that hospital outpatient payments were the second largest cost category, accounting for 19% to 32% of total payments across treatment groups. This was reflected by the changes in treatment patterns observed over the duration of this study and other studies. [108] [148] [147] [172] The high hospital outpatient payments could be attributed to the increased use of immunotherapy, which was usually billed as outpatient services. Additionally, immunotherapy was associated with a longer PFS and OS compared with chemotherapy in previous clinical trials. The lengths of PFS and OS were relevant when evaluating payments, because longer PFS and OS may be accompanied by increased time on treatment and thus, increased healthcare resources utilization and relevant costs. Our study results were consistent with findings from a previous study by Zhang et al. which found that outpatient costs constituted the largest proportion of total costs (\$61,797 of \$158,908 total costs, 38.9%). [172] They also found that outpatient costs for systemic therapy increased over the duration of the study, especially from 2015 when the FDA granted approval for immunotherapies.

We found that the immunotherapy group had 13.37% higher hospital outpatient visit payments while the targeted therapy group had 47.86% lower hospital outpatient visit payments, compared to the chemotherapy group. Higher payments for immunotherapy-treated patients were

also seen in a study by Nesline et al., in which they found significantly higher 6-month reimbursements of outpatient visits in immunotherapy-treated patients compared to patients receiving other therapies (\$31,299 vs. \$77,071). [182] Another study by Haslem et al. assessed costs of targeted therapy between 2013 and 2015 and found that average weekly costs were lower for the targeted therapy group compared to the control group (\$1,167 vs. \$2,376). [186]

4.3.4.5 Prescription payments

Considering the high costs of immunotherapy and targeted therapy, prescription payments were reported as a driver of total healthcare costs in previous studies. [128] [182] [176] [186] In a retrospective by Skinner et al., Medicare-paid costs for anti-cancer therapy accounted for 42.4% of total costs. [128] Another study by Haslem et al. found a significant difference in costs between patients receiving targeted therapy and those receiving chemotherapy or supportive care resulting mainly from patients in the targeted treatment group having higher upfront prescription drug costs. [186] Buck et al. also found that monthly costs for targeted therapy were double those of chemotherapy on average, with up to a 9-fold difference for lung cancer patients in stage IIA/II. [176]

Unlike previous studies, lower proportions of prescription payments were seen in both Medicare-based and commercial insurance-based studies. A recent study by Zhang et al. reported that pharmacy costs accounted for less than 10% of total costs. [172] Similarly, Iadeluca et al. found that prescription payments accounted for a small proportion (11.0%) of total spending in a Medicare-based study. [188] These studies found lower costs in pharmacy and higher costs in the outpatient practice setting.

However, most patients in our study visited hospital outpatient or office settings for their treatments and only 15 patients had lung cancer-related prescriptions from pharmacy claims. Therefore, analysis of prescription payments was not feasible.

4.3.4.6 Home visit and other visit payments

Unlike payments for other healthcare services, we found that the mean payments for home visits were lower for the immunotherapy group (\$348) and higher for the targeted therapy group (\$1,086) compared to the chemotherapy group (\$358). The mean payments for other visits were lower in both the targeted therapy group (\$137) and the immunotherapy group (\$348) compared to the chemotherapy group (\$358). The hurdle model also showed that compared to the chemotherapy group, the immunotherapy group had 23.26% lower home visit payments and 42.7% lower other visit payments; while the targeted therapy group had 131.89% higher home visit payments and 56.54% lower other visit payments. These results suggested that care provided through home visits and other visits are less expensive for lung cancer patients receiving immunotherapy. However, the role of home visit services for patients receiving targeted therapy needs further study.

Payments for home visits and other visits were rarely studied. A study by Iadeluca found that payments for home health care represented for 7.8% of total healthcare payments among Medicare beneficiaries with lung cancer. [188] Haslem et al. reported lower hospice payments in the targeted therapy group than in the chemotherapy and supportive care groups. [186] Inconsistent with our study, Nesline et al, reported mean semiannual payments other than outpatient visits, ER visits, office visits, hospital inpatient visits, and prescription were higher in the immunotherapy group compared to the non-immunotherapy group. [182] The difference could be due to different

populations (Medicaid vs. commercial insurance) and study time period (2014-2021 vs. 2012-2017).

4.3.4.7 Total payments

In summary, the overall payments were primarily driven by payments for office visits and hospital outpatient visits for each treatment group. ER visit payments, home visit payments, and other payments were low, consistent with several previous studies. [186] [97] [182] [183]

Our study found that mean total payments for the immunotherapy group (\$90,179) were much higher than for the chemotherapy group (\$34,620) in descriptive analysis. However, given that not all payments for AE management were included in this study and chemotherapy is more likely to have AEs, different results may have been found if AEs associated with chemotherapy were considered. In addition, the immunotherapy group had 160.93% higher total payments compared to the chemotherapy group in the GLM model. The main drivers of high payments for immunotherapy-treated patients were outpatient visits and office visits, which included drug reimbursement. Our study results were similar to a real-world retrospective study by Nesline et al., in which 6-month total payments in patients receiving immunotherapy (\$141,537) were nearly 2 times higher than payments for those without immunotherapy (\$75,429). [182] Longer PFS and OS associated with immunotherapy may have also contributed to the high payments for patients receiving immunotherapy. Along with results from clinical trials, real-world studies also suggested that immunotherapy significantly increased OS or time on treatment compared to chemotherapy. [182] [179]

A retrospective study by Skinner et al. reported that total Medicare cost was lower in patients who initiated targeted therapy in first line than in those who initiated treatment as second-

line therapy during the treatment period (\$18,354; 95% CI: \$13,929–\$22,781 vs. \$23,221; 95% CI: \$18,660–\$27,782; $p=0.002$). [128] However, during the post-disease progression period, the mean monthly cost was lower in patients who initiated targeted therapy as second-line therapy than in those who initiated TKI as first-line therapy (\$21,930; 95% CI: \$16,399–\$27,460 vs. 14,158; 95% CI: \$9,757–\$18,560; $p=0.011$). Thus, it would be helpful to assess the total cost incurred over the entire observation period. Another study by Haslem et al. also found that average costs over the entire study period were significantly lower for the targeted treatment group compared to the control group who had received standard chemotherapy or best supportive care (\$2,720 per week vs. \$3,453 per week, $p=0.036$). [186] Their study further found that patients with late-stage cancer who received a targeted therapy had 6.9% lower costs in the last 3 months of life compared with those who did not. Our study found that mean total payments for the targeted therapy (\$23,287) were lower than those for the chemotherapy group (\$34,620). The GLM model showed that the targeted therapy group was associated with lower total payments, although the relationship was not significant. Considering the improvement in survival outcomes in clinical trials and real-world studies, targeted therapy may be the preferred treatment option for patients with lung cancer. [186]

4.4 Limitations

This study has some limitations to consider. As with other retrospective claims-based studies, it was not possible to capture disease histology, disease stage, patient performance status, biomarker status, and other clinical characteristics. Because of lack of information regarding disease histology, we cannot distinguish between SCLC and NSCLC. Although we excluded patients receiving topotecan or temozolomide for SCLC during the pre-index period, we couldn't

confirm that the study population consisted of NSCLC patients since many of the same medications are prescribed for SCLC and NSCLC patients. However, considering that NSCLC accounts for nearly 85% of lung cancer patients, it is highly likely that NSCLC patients would account for most of the study population. Furthermore, the low proportion of patients receiving treatments (39%) seen in this study may have resulted from some patients being in early-stage disease where systemic treatments are not necessary. According to the NCCN guideline, the initial treatment for patients in early stage (stage I, stage II, and stage IIIA) is surgical exploration and resection. Chemotherapy is recommended only for high-risk early-stage patients; targeted therapy and immunotherapy are recommended for advanced or metastatic lung cancer. We could not identify disease stages using Medicaid data. However, underuse of treatment for lung cancer has been noted in the literature. [92, 93, 94, 96] [102] Another potential limitation is that patients may have received care covered by other payers (e.g., Medicare) or paid out-of-pocket. Also, data entry errors in claims submissions might occur. It is possible that data regarding visits, payments, and demographic characteristics may have been inaccurate for some enrollees.

The definition of treatment line used in this study did not strictly follow the medical definition (disease progression) since no clinical records were present in the claims database and thus, we used a definition similar to that used in the literature. This may have caused treatments to be classified into a new treatment line even though progression had not occurred. Additionally, this research categorized patients into different treatment groups based on their initial treatment, which may lead to two issues. First, each treatment group included patients receiving either monotherapy or combination therapy. For example, if a patient received immunotherapy in combination with chemotherapy, they would be classified into the immunotherapy group for evaluation. Combination therapy was likely to incur higher costs compared to monotherapy.

Second, we evaluated payments during a 1-year follow-up period, including payments for first-line treatment and subsequent-line treatment. Once a patient switches to a different treatment group in the subsequent line, the payments were influenced by more than just a “pure” treatment group. For example, we observed that a portion of patients initially receiving chemotherapy in the first line received immunotherapy in the subsequent line. As a result, the payments of the chemotherapy group will be affected by the addition of immunotherapy in the subsequent line.

This study estimated healthcare resource utilization and payments only for medical claims with lung cancer-specific diagnosis and procedure codes. AE management, especially for chemotherapy, is recognized as an important driver of hospitalization and ER visits, but AE management visits were not easily identified. The payments may be underestimated if a patient had medical services due to treatment-related adverse reactions but did not have a confirmed diagnosis of lung cancer. Considering that chemotherapy drugs are more likely to cause adverse reactions compared to immunotherapy or targeted therapy medications, the actual treatment payments (if AE payments had been included) in the chemotherapy group may be higher than what was observed in this study. Therefore, the results should be interpreted with caution.

Potential challenges regarding the zero-inflated model used for objective 3 should be noted. Analyses could not be conducted for hospitalization and home visits because the models did not converge, which was probably due to the small number of patients with health services utilization by treatment groups. Additionally, multicollinearity was present in these analyses. Thus, we provided descriptive analyses only. We also noticed that the results for some covariates (e.g., Charlson Comorbidity Index in objective 5) were counterintuitive in our study. With the relatively small number of patients who had hospitalization or home visits, the coefficients may be unstable. These counterintuitive results could also possibly be due to interactions with other variables.

Finally, this study focused on the lung cancer patients enrolled in Texas Medicaid, and therefore, may not be generalizable to other populations.

4.5 Potential implications

This study provides insight regarding treatment patterns, the utilization of healthcare services, and the payments for those services in the treatment of lung cancer in Texas Medicaid enrollees. The results may help payers, policy makers, and healthcare providers identify areas for improvement in the management of lung cancer among Texas Medicaid enrollees, and further improve population health and reduce costs.

First, our study results confirmed that the lung cancer treatment landscape has evolved with immunotherapy becoming more common place in the treatment of lung cancer. We found that immunotherapy was more often preferred as second-line treatment, although it has been approved for first-line treatment for years and recommended by the NCCN guidelines. This suggests that health providers may be hesitant to choose immunotherapy as first-line treatment. A possible reason could be that chemotherapy has been used for more than 40 years with accumulating evidence of effectiveness and healthcare providers are more familiar with the use of chemotherapy and the management of related adverse reactions. On the other hand, the study time frame was July 2014 to June 2021 which allowed only 2 to 3 years of observation after FDA approval for PD-(L)1 for first-line treatment for lung cancer. During that period, immunotherapy was still relatively new with limited real-world practice experience regarding effectiveness and management of related adverse events, some of which may be severe. However, immunotherapy has generally been perceived as a promising treatment option by health providers. [189] Thus, education and training focusing on the dissemination and interpretation of long-term clinical/real-world data pertaining

to immunotherapy is needed. Given the significant improvement in survival outcomes shown in clinical trials and recently published real-world studies, we believe that encouraging appropriate use of immunotherapy in suitable patients will help to improve lung cancer patients' health outcomes. In addition, patient education is also necessary since some patients may be concerned that side-effects may affect their quality of life and thus, refuse to accept treatment with immunotherapy. Helping patients to better understand their treatment options could not only help patients cope with side effects, but also be more proactive in their treatment, leading to better treatment outcomes.

Second, we found only a few patients receiving targeted therapy even though it has been available for use for many years, which indicates that it may be underused among Texas Medicaid enrollees. One possible explanation is that Medicaid did not cover comprehensive biomarker testing and in turn, patients are not able to afford the high out-of-pocket costs for the testing. [190] Biomarker testing is an important way to identify patients whose survival could be significantly prolonged with the right therapy. Considering the clinical benefits of biomarker testing, the Centers for Medicare & Medicaid Services (CMS) issued a national coverage determination and local coverage determination that increased access to biomarker testing for Medicare beneficiaries in 2020 and 2022, respectively. Many states, including Arizona, California, Illinois, have passed laws to mandate coverage for biomarker testing. Covering biomarker testing could add an economic burden to the government, but it is also important to ensure that Medicaid patients have access to treatments. Thus, the policy makers in Texas could review the experiences in other states and develop a strategy to balance the risks and benefits.

Third, increasing use of immunotherapy shown in our study and previous studies, as well as additional approvals of new therapies may increase the financial burden for state governments

in providing services for patients covered by Medicaid. [147] [148] [172] As noted in our study, office visits and hospital outpatient visits were primary drivers of total payments, highlighting the importance of improving quality of care, as well as providing incentives for managing utilization and payments appropriately.

4.6 Future studies

This study identified several areas worthy of further research. First, Dr. Kenny Nguyen mentioned in his email that immunotherapy has been used more commonly in first-line treatment during the last 2 years at Texas Oncology. It would be valuable to continuously evaluate changes in treatment patterns, as well as payments for Texas Medicaid patients. Second, studying factors associated with treatment selection is important to help payers identify patients who are more likely to benefit from the treatment. Third, although our study showed that immunotherapy is associated with higher payments, it still could be a cost-effective treatment compared to traditional chemotherapy. Future studies should investigate if and to what extent innovative treatment could improve long-term survival to provide more information on treatment selection for clinicians and payers.

4.7 Conclusions

To our knowledge, this is the first study comparing treatment patterns, healthcare resource utilization, and payments associated with chemotherapy, targeted therapy, and immunotherapy. This study used the most recent data available in Texas Medicaid, addressing existing gaps in the literature. Most previous studies are either Medicare-based studies which focus on the elderly population, or commercial-based studies in which patients may have easier access to care. The

sample for this study was younger than samples in Medicare-based studies, thus capturing utilization and payment information for younger lung cancer patients, an area with little previous literature. Few previous studies included targeted therapy and immunotherapy, and for studies that included those treatments, only selected targeted therapies or immunotherapies were assessed. Finally, few studies have assessed healthcare resource utilization and payments by types of health services using advanced models.

This study adds to the growing body of evidence of transformation in the treatment landscape of lung cancer. Our study confirmed greater use of immunotherapy and targeted therapy, especially in subsequent line, indicating growing adoption in clinical practice. The economic burden of lung cancer is still heavy. We also found that office visits and outpatient visits were primary drivers of lung cancer-related payments, highlighting the need for more attention to address high-cost services provided in outpatient and office practice settings. Although, compared to chemotherapy, immunotherapy had similar or even lower numbers of ED visits, office visits, and hospital outpatient visits after controlling for covariates, it still associated with a higher total payment mainly because of higher payments for office visits and hospital visits. This result raises a concern about the high cost of immunotherapy which may further increase the economic burden for Texas Medicaid. However, lower healthcare resource utilization associated with targeted therapy may offset increased treatment costs leading to lower total payments. Thus, targeted therapy could be an attractive treatment option for lung cancer patients.

The results of this study can be used to help healthcare providers, policy makers, and payers better understand the current status of management of lung cancer and prepare for the future.

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