Effectiveness, Safety, and Cost-Effectiveness of Immune Checkpoint Inhibitors for Metastatic Non-Small Cell Lung Cancer: Leveraging Real-World Evidence

by

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Abstract

Objective: The purpose of this doctoral dissertation project was to 1) compare the effectiveness of first-line individual immune checkpoint inhibitor (ICI) agents and ICI in combination with chemotherapy (ICI-Chemotherapy) versus ICI monotherapy (ICI-Monotherapy) for patients with metastatic non-small cell lung cancer (mNSCLC), 2) develop regression and machine learning (ML) models for the prediction of immune-related adverse events (irAEs), and 3) evaluate the cost-effectiveness of first-line cemiplimab plus chemotherapy (CCT) compared to pembrolizumab plus chemotherapy (PCT).

Methods: For Aims 1 and 2, we used the 2014–2020 Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked database. In aim 1, we designed a new-user cohort to compare the effectiveness of first-line atezolizumab, nivolumab, and pembrolizumab among older adults with mNSCLC. Overall survival (OS) was compared using unadjusted, multivariable-adjusted, and propensity score matching (PSM) Cox proportional hazards models. Additionally, we emulated two hypothetical target trials to compare OS between first-line ICI-Monotherapy and ICI-Chemotherapy, and 4 versus 6 cycles of chemotherapy within the first-line ICI-Chemotherapy regimens. The clone-censor-weight approach and discrete-time hazards model were applied to estimate the per-protocol treatment effects. OS was evaluated through survival curves, 72-week OS probabilities,72-week restricted mean survival time (RMST), and hazard ratios (HR). In aim 2, given the suboptimal performance of models in predicting overall irAEs, we systematically evaluated predictive performance across irAE subtypes, ultimately focusing on endocrine-related irAEs. Patients with mNSCLC treated with first-line ICIs were randomly divided into training (80%) and testing (20%) sets. We developed the Least Absolute Shrinkage and Selection Operator (LASSO) and ML approaches, including random forest,

support vector machines, and XGBoost, to predict 3-month endocrine-related irAEs. Model performance was evaluated using accuracy, F1 score, and the area under the receiver operating characteristic curve (AUROC) in the test set. In aim 3, a three-state partitioned survival model with a 10-year time horizon was constructed. Clinical data were sourced from the EMPOWER-Lung 3, KEYNOTE-407, and KEYNOTE-189 trials. Costs and quality of life inputs were obtained from the 2024 U.S. Centers for Medicare & Medicaid Services drug price lists and published literature. We calculated the total cost, quality-adjusted life-years (QALYs) gained, and the incremental cost-effectiveness ratio (ICER).

Results: Pembrolizumab was associated with a significant survival benefit compared to atezolizumab (multivariable-adjusted HR=0.67; 95% confidence interval (CI)=0.53-0.84; PSM HR=0.69; 95% CI=0.54-0.87) and nivolumab (multivariable-adjusted HR=0.83; 95% CI=0.69-0.99). In the per-protocol analysis of emulated target trials, ICI-Chemotherapy provided a marked OS advantage over ICI-Monotherapy, including a 5.5% higher 72-week OS rate (95% CI=4.2%-6.7%), a 6.27-week additional RMST gain (95% CI=4.88-7.61), and HR=0.76 (95% CI=0.71-0.81). Patients receiving 6 versus 4 cycles of chemotherapy had a 5.1% (95% CI=–0.9%–11.0%) higher 72-week OS rate, a 2.19-week additional RMST gain (95% CI=0.54–4.92), and an HR of 0.83 (95% CI=0.65–0.95). The LASSO model outperformed other ML models to predict 3-month endocrine-related irAEs, achieving an accuracy of 0.791 (95% CI=0.789–0.793), an F1 score of 0.507 (95% CI=0.502–0.512), and an AUROC of 0.724 (95% CI=0.719–0.728). The most important predictors identified included pre-existing endocrine disorders, type 2 diabetes, use of atezolizumab, concurrent chemotherapy, and patient demographics. In the cost-effectiveness analysis, the total cost of PCT was $207,926 with 1.609 QALYs, whereas CCT had

a total cost of $175,247 with 1.657 QALYs, indicating that CCT was a dominant first-line treatment strategy over PCT (ICER=−$675,304 per QALY) for patients with mNSCLC.

Conclusion: Pembrolizumab was associated with a significant OS benefit compared with atezolizumab and nivolumab among older adults with mNSCLC. Adding chemotherapy to first-line ICI therapy offered additional survival benefits over ICI-Monotherapy, and extending chemotherapy from 4 to 6 cycles was associated with additional improvements in survival outcomes. The LASSO model demonstrated the best performance in predicting endocrine-related irAEs using SEER-Medicare data. Compared with PCT, CCT was a dominant first-line treatment option for mNSCLC from a cost-effectiveness perspective.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

ICI	Immune Checkpoint Inhibitor
MNSCLC	Metastatic Non-Small Cell Lung Cancer
PD-L1	Programmed Death-Ligand 1
SEER	Surveillance, Epidemiology, and End Results
OS	Overall Survival
IrAEs	Immune-related Adverse Events
PCT	Pembrolizumab Plus Chemotherapy
CCT	Cemiplimab Plus Chemotherapy
KM	Kaplan–Meier
CPH	Cox Proportional Hazards
HR	Hazard Ratio
RMST	Restricted Mean Survival Time
SIPCW	Stabilized Inverse Probability of Censoring Weights
LASSO	Least Absolute Shrinkage and Selection Operator
ML	Machine Learning
ICER	Incremental Cost-Effectiveness Ratio

Chapter 1: Introduction

1.1. Overview of immunotherapy for patients with metastatic non-small cell lung cancer

Lung cancer is the second most prevalent cancer and the primary cause of cancer-related mortality in both men and women in the United States (U.S.) (not counting skin cancer).[1] In 2023, there were 238,340 new cases of lung cancer and 127,070 fatalities in the U.S., accounting for 12.2% of total cancer incidence and 20.8% of cancer deaths.[1, 2] The types of lung cancer are mainly categorized into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) based on histology. NSCLC accounts for 80-85% of lung cancer cases.[3] Around 70% of patients with lung cancer are already in advanced or metastatic stages at the time of diagnosis.[4] The five-year relative survival rate is only 9% for metastatic non-small cell lung cancer (mNSCLC).[4] Immunotherapy has significantly improved the survival outcomes in patients with NSCLC. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that block specific proteins on immune cells and cancer cells, enhancing the immune system's ability to recognize and eliminate cancer cells.[5] The specific proteins include programmed death-1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).[6, 7] In March 2015, nivolumab was approved by the Food and Drug Administration (FDA) as the first ICI to treat mNSCLC.[8] Since then, seven ICIs (nivolumab, pembrolizumab, cemiplimab, atezolizumab, durvalumab, ipilimumab, and tremelimumab) have been approved and launched as first-line treatments for mNSCLC.[7] The adoption of ICI treatments increased significantly for patients with lung cancer.[9] In the U.S., the proportion of lung cancer patients receiving immunotherapies increased by 26.5% from 2018 to 2021, reaching 62%.[10] However, the distinctive mechanism of immunotherapy that exerts anti-tumor effects also determines their unique toxicity profiles. The reported incidence of immune-related adverse events (irAEs) ranged from 30% to 49% in cancer

patients treated with ICIs.[11-13] Immunotherapy also imposes a substantial financial burden on patients due to its high cost.[14, 15] In 2021, the average annual drug cost for patients undergoing immunotherapy in the U.S. was $132,582, significantly surpassing the $26,095 for patients who did not receive immunotherapy.[16] Even though only 12.1% of cancer patients received immunotherapy, the expenditure on immunotherapy accounted for 36.2% of total oncology medication spending.[16]

The current literature has the following five main knowledge gaps in the management of patients with mNSCLC receiving immunotherapy:

a) The efficacy/effectiveness of ICIs has been evaluated primarily in comparison to chemotherapy.[17-26] The most effective ICI for achieving optimal survival outcomes remains unclear due to the absence of head-to-head trials and longitudinal studies.
b) Whether adding chemotherapy to first-line ICI regimens can improve the survival outcome in patients with mNSCLC is still debatable.
c) The survival benefit of extending chemotherapy from 4 to 6 cycles remains uncertain in patients with mNSCLC treated with first-line ICI-Chemotherapy.
d) Existing machine learning (ML) models for predicting irAEs either did not explicitly focus on mNSCLC, were limited by small sample sizes, or had insufficiently selected predictive features.[27, 28] The limitations of these predictive models constrain their applicability to mNSCLC.
e) Among existing ICI treatment regimens, pembrolizumab combined with chemotherapy (PCT) is considered the preferred first-line treatment for mNSCLC patients regardless of PD-L1 level from a cost-effective perspective.[16] The cost-effectiveness of the newly

approved cemiplimab combined with chemotherapy (CCT) compared to the PCT remains unknown and warrants further investigation.

1.2. Overall objectives of the doctoral dissertation project

This doctoral dissertation study aims to provide new, real-world evidence on the effectiveness, safety, and cost-effectiveness of ICIs for patients with mNSCLC. This project is among the first to compare the effectiveness of individual ICI agents, ICI-Chemotherapy versus ICI-Monotherapy, and 4 versus 6 cycles of chemotherapy in ICI-Chemotherapy regimens; to predict irAEs risk using LASSO and ML approaches; and to assess the cost-effectiveness of newly approved CCT compared to PCT as the first-line treatment. The evidence generated from this dissertation could inform and support clinical practice in the use of ICIs for mNSCLC.

1.3. Specific aims

Aim 1. To compare the effectiveness of individual ICIs and of ICI–Chemotherapy versus ICI-Monotherapy as first-line treatment in patients with mNSCLC.

We conducted a retrospective new user cohort study to compare three marketed ICIs, including pembrolizumab, atezolizumab, and nivolumab on survival outcomes. First-line ICI treatment was defined as the initiation of ICIs in previously untreated patients following their diagnosis. A six-month washout period before diagnosis was used to exclude patients who received any cancer treatments before cancer diagnosis. The primary outcome is overall survival (OS), which is defined as the time from first-line ICI treatment initiation to death. OS was compared using unadjusted, multivariable-adjusted, and propensity score matching (PSM) Cox proportional

hazards (CPH) models. We also emulated two hypothetical target trials to compare the OS between (1) first-line ICI-Chemotherapy vs. ICI-Monotherapy and (2) 4 vs. 6 cycles of chemotherapy for patients in first-line ICI-Chemotherapy regimens. We applied a clone-censor-weight approach to address potential immortal time bias and treatment non-adherence in per-protocol analysis. Discrete-time hazards model was used to estimate time-varying treatment effects. OS was evaluated via survival curves, 72-week survival probabilities, restricted mean survival times (RMST), and hazard ratios (HR).

Aim 2. To develop machine learning models for the prediction of irAEs after ICI initiation among patients with mNSCLC.

Given that most irAEs occur within three months of ICI treatment initiation, the primary outcome was the occurrence of irAEs (i.e., pneumonitis, arthritis, etc.) during this period.[29] Gastrointestinal (GI) irAEs, such as diarrhea, colitis, and hepatitis, are among the most frequent and severe irAEs observed with ICI treatments.[30] Pneumonitis was identified as the most frequent irAE for patients with NSCLC after ICI treatments.[31] The secondary outcomes were the occurrence of pneumonitis and GI irAEs within three months after first-line ICI initiation.[31, 32] Predicting features included patient demographics, socioeconomic status, comorbidities, time from diagnosis to ICI initiation, ICI agents, other cancer treatments, and other pre-existing conditions. We randomly split the 2014—2020 Surveillance, Epidemiology, and End Results (SEER)—Medicare data into training (80%) and test (20%) sets. To develop prediction models, we applied the least absolute shrinkage and selection operator (LASSO) logistic regression and three ML algorithms: random forest (RF), support vector machine (SVM) with a radial basis function kernel, and extreme gradient boosting (XGBoost). Model performance was evaluated using the test set.

Aim 3. To compare the cost-effectiveness of first-line cemiplimab plus chemotherapy with pembrolizumab plus chemotherapy for mNSCLC patients.

From the healthcare payer perspective, we developed a partitioned survival model to estimate the cost-effectiveness of CCT as the first-line treatment for patients with mNSCLC compared to PCT.[20, 33] The partitioned survival model was designed from progression-free survival (PFS) to disease progression (PD) and ultimately to death. The survival and adverse event (AE) incidence were derived from the EMPOWER-Lung 3, KEYNOTE-407, and KEYNOTE-189 trials. [20, 23, 34-38] Treatment costs were obtained from the Centers for Medicare & Medicaid Services April 2024 Part B Drug Average Sales Price file.[39] Other parameters, such as the cost of AEs and patients' utilities at different progression stages, were obtained from published literature.[40-44] The main outcomes included costs, quality-adjusted life-year (QALYs), and incremental cost-effectiveness ratio (ICER).

1.4. Significance of the project

The FDA approved ICI treatment regimens based on evidence from phase III clinical trials demonstrating superior survival outcomes compared to chemotherapy alone.[17-26, 45] The most effective ICI for achieving optimal survival benefit remains unclear due to the absence of head-to-head trials and longitudinal studies. Aim 1 of this dissertation project addressed this critical knowledge gap by conducting a head-to-head comparison of first-line ICI treatments on survival outcomes for mNSCLC using real-world data. The findings offered vital information about the comparative effectiveness of different ICI treatments, supporting informed decision-making for both patients and clinicians.

In addition, the optimal use of first-line ICI in combination with chemotherapy for mNSCLC remains uncertain. Question persists regarding the necessity and benefit of continuing chemotherapy from 4 to 6 cycles in patients who initiated first-line ICI-Chemotherapy regimens. Therefore, aim 1 also emulated two target trials to evaluate: (1) the comparative OS between ICI-Monotherapy and ICI-Chemotherapy, and (2) the OS between 4-cycle and 6-cycle chemotherapy regimens within the first-line ICI-Chemotherapy regimen. The results could provide crucial evidence to support future refinement of treatment guidelines and support the selection of therapies that offer the greatest clinical benefit.

IrAEs pose an increased risk of morbidity, discontinuation of treatment, and even death in rare cases.[46] Aim 2 of this dissertation comprehensively evaluated risk factors and developed tailored predictive models for irAEs in the context of mNSCLC. The predictive model could assist healthcare providers and patients in anticipating and managing irAEs, enhancing the safety, continuity, and personalization of ICI therapy for mNSCLC.

Lastly, given the extremely high price of ICI treatments, evaluating their cost-effectiveness is essential for informing treatment decisions for both patients and the healthcare system. Aim 3 evaluated the cost-effectiveness of newly marketed CCT compared to PCT as the first-line treatment for patients with mNSCLC. The findings could guide patients in balancing financial burden with treatment outcomes, while also supporting healthcare professionals and policymakers to make evidence-based decisions in insurance coverage and resource allocation.

Overall, the findings of this dissertation provided comprehensive and up-to-date real-world evidence on the effectiveness, safety, and cost-effectiveness of ICI treatments for patients with

mNSCLC. The generated evidence could guide clinical decision-making and inform formulary development in the constantly evolving landscape of mNSCLC care.

Chapter 2: Literature review

2.1. Lung cancer: burden of the disease in the United States

2.1.1. Prevalence, incidence, and mortality

Lung cancer is the second most prevalent malignancy and the leading cause of cancer-related mortality in the U.S.[47] According to the United States Cancer Statistics (USCS), there were 238,340 new cases of lung cancer and 127,070 lung cancer-related fatalities in 2023, comprising 12.2% of total cancer incidence and 20.8% of cancer deaths.[1, 2] Based on the data from the SEER Programs in 2017-2019, the lifetime probability of being diagnosed with lung cancer was 6.1%.[2] About 53% of individuals diagnosed with lung cancer are 70 or older, and 83% of cases are diagnosed at 65 or older. Only 2.1% of patients diagnosed with lung cancer are younger than 45 years old.[4, 48, 49]

The rate of incidence and mortality of lung cancer exhibited a consistent decline in the U.S.[50] The age-adjusted rates for new cases of lung cancer had decreased by an average of 2.0% per year from 2010 to 2019.[50] The age-adjusted death rates had decreased by an average of 4.1% per year from 2011 to 2020.[50] According to the American Cancer Society, the five-year relative survival rate for all types of lung cancer is 25.4%. Separately, the five-year relative survival rate is 28% for NSCLC and 7% for SCLC.[51] The survival rate also varies depending on the cancer stages. The five-year relative survival rate for patients with NSCLC is 65% for the localized stage, 37% for the regional stage, and 9% for the distant stage.[51] The five-year relative survival rate for patients with SCLC is 30% for the localized stage, 18% for the regional stage, and 3% for the distant stage. However, at the time of diagnosis, around 70% of patients with lung cancer are already in advanced or metastatic stages.[4]

2.1.2. Types, symptoms, and causes of lung cancer

Lung cancers are mainly categorized into two types, NSCLC and SCLC. NSCLC accounts for 80-85% of lung cancer cases. Within NSCLC, there are three subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. SCLC comprised 10% to 15% lung cancer cases.[3] Notably, SCLC grows and spreads more aggressively, and has a higher rate of recurrence than NSCLC. In addition to SCLC and NSCLC, other types of lung cancer are rare, such as lung carcinoid tumors, adenoid cystic carcinomas, lymphomas, and sarcomas, accounting for fewer than 5% of cases.[3]

Most lung cancer cases remain asymptomatic until they have spread, though some patients at the early stage do have symptoms.[52, 53] The most common symptoms of lung cancer are cough, coughing up blood, chest pain, and hoarseness (Table 1).[52-54] As the malignancy progresses and metastasizes, patients may suffer from bone pain, nervous system changes, yellowing of the skin and eyes, and swelling of lymph nodes.[52-54]

In addition, lung cancer may cause certain syndromes, including Horner syndrome, Superior vena cava symptoms, and Paraneoplastic syndromes.[52, 53] Horner syndromes are characterized by the drooping or weakness of one upper eyelid, a smaller pupil in the same eye, or little to no sweating on the same side of the face. Superior vena cava symptoms can occur when the tumor is located in the upper part of the right lung and the lymph nodes inside the chest.[52, 53] The pressure on the superior vena cava leads to the backward flow of blood in veins. Paraneoplastic syndromes are caused by the hormone-like substances produced by the cancer cells.[52] These substances enter the bloodstream, affecting distant tissues and organs, causing conditions like the syndrome of inappropriate anti-diuretic hormone and Cushing syndrome.[52]

The causes and risk factors for SCLC and NSCLC are similar, with smoking cigarettes being the predominant factor. Smoking cigarettes could explain almost 90% of lung cancer risk in men and 70-80% in women.[55, 56] Frequent exposure to other people's tobacco smoke can also increase the risk of developing lung cancer. However, it's important to note that people who have never smoked can also develop lung cancer. Besides smoking, as summarized by the National Health Service (NHS) and American Cancer Society, factors that may cause lung cancer include exposure to radon gas, carcinogens, and other air pollution, family history, and certain lung diseases.[55, 56]

Table 1. Common symptoms in lung cancer patients

A cough that does not go away or gets worse
Coughing up blood or rust-colored sputum (spit or phlegm)
Chest pain that is often worse with deep breathing, coughing, or laughing
Hoarseness
Loss of appetite
Unexplained weight loss
Shortness of breath
Feeling tired or weak
Infections such as bronchitis and pneumonia that don't go away or keep coming back
New onset of wheezing

2.1.3. Economic burden of lung cancer

The cost of treating lung cancers can vary depending on several factors, including the disease's stage, the type of treatments, and insurance coverage. Based on a systematic review, lung-cancer-related healthcare costs for SCLC per patient were $44,167, and $70,548 for all-cause healthcare costs in 2018.[57] The lung cancer-related healthcare costs for NSCLC per patient were $37,932, and $67,175 for all-cause healthcare costs, significantly lower than the SCLC cost.[57] The cost of treating lung cancer has increased over the years. In 2021, Zhang et al. found that the mean cost for advanced or mNSCLC had increased to $158,908 per patient per year, including $61,797 for the outpatient systemic anticancer treatment, and $27,138 for the first-line treatment in the U.S.[9] The high cost of lung cancer treatment also puts a substantial economic burden on the healthcare system. For example, Joshua et al. found that the overall cost for programmed cell death ligand 1 (PD-L1) positive stage IV NSCLC in the U.S. in 2019 was $3.01 billion, with 97% ($2.91 billion) in drug expenses.[58]

2.2. Immunotherapy for mNSCLC

2.2.1. Mechanisms of immune checkpoint inhibitors

The decline in the fatality rate of NSCLC is related to the development of effective treatments.[59] Immunotherapies are designed to enhance the immune system's ability to fight cancer, and they have become pivotal treatments for NSCLC patients with a notable increase in their adoption.[9] In 2021, 62% of lung cancer patients received immunotherapies, a 26.5% increase since 2018.[10] ICIs work by blocking specific checkpoint proteins on cancer and immune cells, including PD-1, PD-L1, and CTLA-4.[6, 7] By doing so, ICIs enhance the immune system's ability to recognize and

eliminate cancer cells. In March 2015, nivolumab was approved by the FDA as the first ICI for treating advanced or mNSCLC in patients with disease progression after platinum-based chemotherapy.[8] Since then, seven ICIs have been launched as first or second-line treatments for mNSCLC (including nivolumab, pembrolizumab, cemiplimab, atezolizumab, durvalumab, ipilimumab, and tremelimumab).[7] Table 2 presents the nonproprietary and proprietary names of ICIs, along with their FDA approval dates for first-line treatment of mNSCLC, and corresponding U.S. marketing dates.

Table 2. Immune checkpoint inhibitors approved for the treatment of metastatic non-small cell lung cancer

Target	Function	Nonproprietary Name	Proprietary Name	FDA Approval Date	Marketing Date
PD-1	Blocks PD-1 on immune cells (T cells) to enhance the immune response against cancer cells.	Nivolumab	Opdivo®	May 15, 2020	December 22, 2014
		Pembrolizumab	Keytruda®	October 2, 2015	January 15, 2015
		Cemiplimab	Libtayo®	February 22, 2021	September 28, 2018
PD-L1	Blocks PD-L1 on some tumor cells and immune cells to boost the immune response against cancer cells, leading to tumor shrinkage or slowed growth.	Atezolizumab	Tecentriq®	December 3, 2019	May 18, 2016
		Durvalumab	Imfinzi®	November 10, 2022	May 1, 2017
CTLA-4	Blocks CTLA-4 on T cells, enabling the immune system to selectively check foreign invaders or harmful cells and attack cancer cells.	Ipilimumab	Yervoy®	May 15, 2020	March 25, 2011
		Tremelimumab	Imjudo®	November 10, 2022	October 21, 2022

2.2.2. Indications of ICIs for mNSCLC

As this dissertation focused on mNSCLC, the approved first-line immunotherapies for mNSCLC patients are summarized in Table 3:[59]

- Pembrolizumab, atezolizumab, or cemiplimab can be used as first-line treatment for mNSCLC patients with PD-L1≥50%.
- Pembrolizumab, atezolizumab, or cemiplimab, when combined with chemotherapy, can be used for mNSCLC patients, regardless of PD-L1 levels.
- Ipilimumab with nivolumab or tremelimumab with durvalumab, in combination with chemotherapy, are also approved as the first-line treatment for patients with advanced/mNSCLC.

Table 3. Approved first-line ICI regimens for mNSCLC by PD-L1 expression level

PD-L1 ≥50% First-line Therapy	**PD-L1 ≥1%–49% First-line Therapy**	**PD<1%(negative) First-line Therapy**
For non-squamous and squamous NSCLC		
Pembrolizumab	Pembrolizumab*	(Carboplatin or cisplatin) + pemetrexed + pembrolizumab
(Carboplatin or cisplatin) + pemetrexed + pembrolizumab	(Carboplatin or cisplatin) + pemetrexed + pembrolizumab	
Atezolizumab		
Cemiplimab-rwlc		
Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin)	Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin)	Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin)
Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel	Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel	Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel
Nivolumab + ipilimumab	Nivolumab + ipilimumab	Nivolumab + ipilimumab
For non-squamous NSCLC		
Carboplatin + paclitaxel + bevacizumab + atezolizumab	Carboplatin + paclitaxel + bevacizumab + atezolizumab	Carboplatin + paclitaxel + bevacizumab + atezolizumab
Carboplatin + albumin-bound paclitaxel + atezolizumab	Carboplatin + albumin-bound paclitaxel + atezolizumab	Carboplatin + albumin-bound paclitaxel + atezolizumab

Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin)	Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin)	Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin)
Cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin)		
Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed	Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed	Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed
For squamous NSCLC		
	Cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin)	Cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin)
Remelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine	Remelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine	Remelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine
Nivolumab + ipilimumab + paclitaxel + carboplatin	Nivolumab + ipilimumab + paclitaxel + carboplatin	Nivolumab + ipilimumab + paclitaxel + carboplatin

ICI: Immune checkpoint inhibitor; PD-L1: programmed cell death ligand 1

*: used in certain circumstances

2.2.3. Cost of ICIs for mNSCLC

Immunotherapy stands out as an effective but expensive cancer treatment. In 2021 in the U.S., the average drug cost for patients undergoing immunotherapy was $132,582 per year, significantly surpassing the cost for patients who did not receive immunotherapy ($26,095).[16] The average cost per patient receiving immunotherapy is five times greater than receiving other anticancer therapies.[16] Although only 12.1% of all types of cancer patients received immunotherapy, it accounts for 36.2% of oncology medication spending.[16] The average spending per patient in 2021 for each ICI, based on the Centers for Medicare & Medicaid Services (CMS), is listed in Table 4.[60]

Table 4. The average spending per patient on individual ICIs in Medicare Part B in 2021

ICI drugs	Drug	Average spending in 2021
PD-1	Pembrolizumab	$63,131
PD-1	Cemiplimab	$66,372
PD-1	Nivolumab	$61,890
PD-L1	Durvalumab	$49,988
PD-L1	Atezolizumab	$52,152
CTLA-4 inhibitor	Ipilimumab	$53,089
CTLA-4 inhibitor	Durvalumab	$49,988

ICI: Immune checkpoint inhibitors; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; CTLA-4: cytotoxic T-lymphocyte associated protein 4

2.3. Efficacy and effectiveness of ICIs for mNSCLC from clinical trials and real-world evidence

The approvals of ICIs for mNSCLC were based on rigorous clinical trials compared to chemotherapy alone. Table 5 summarizes the evidence from clinical trials supporting the approvals of ICIs as the first-line treatment for mNSCLC patients.

In the "KEYNOTE" series trials, pembrolizumab's efficacy underwent rigorous examination. The KEYNOTE-024 trial compared single-agent pembrolizumab (pembrolizumab-monotherapy) against chemotherapy for patients with advanced non-squamous and squamous NSCLC with PD-L1expression ≥ 50%.[19, 35, 36] The study found that patients treated with pembrolizumab had a significant increase in median PFS compared to those treated with chemotherapy (10.3 months vs. 6 months, HR = 0.50; 95% confidence interval (CI), 0.3–0.68; p < 0.001). Furthermore, the median OS also demonstrated the enduring benefits of pembrolizumab, as the OS reached 26.3 months compared to 13.4 months in the chemotherapy group.

Similarly, the KEYNOTE-042 trial illuminated the substantial therapeutic advantages of pembrolizumab-monotherapy over chemotherapy in advanced non-squamous and squamous NSCLC patients with PD-L1expression ≥ 50%.[34] The OS of the pembrolizumab group was prolonged for 7.8 months (20.0 months vs. 12.2 months, HR = 0.69; 95% CI, 0.56–0.85; p = 0.0003). In contrast, the trial showed no significant difference in OS between pembrolizumab and chemotherapy (HR = 0.92; 95% CI, 0.77–2.11) for patients with lower PD-L1 expression (1% to 49%).

Meanwhile, the KEYNOTE-189 study revealed outcomes in PCT versus chemotherapy alone for metastatic non-squamous patients regardless of PD-L1 levels.[23] These outcomes

included a heightened one-year survival rate of 69.2% compared to 49.4% (HR = 0.49; 95% CI, 0.38–0.64)), an extended PFS (8.8 months vs. 4.9 months, HR = 0.52; 95% CI, 0.43–0.64), and a comparable incidence of severe AEs (67.2% vs. 65.8%).[23]

In the KEYNOTE-407 trial for metastatic squamous NSCLC, PCT exhibited notable improvements in patient outcomes compared to chemotherapy alone.[38] Regardless of PD-L1 expression, the PCT group demonstrated a significant extension in OS (15.9 months vs. 12.3 months, HR = 0.64; 95% CI, 0.49–0.85) and PFS (6.4 months vs. 4.8 months, HR = 0.56; 95% CI, 0.45–0.70).[38]

The “IMpower" series trials represent a comprehensive examination of the therapeutic efficacy of atezolizumab. In IMpower 110, atezolizumab was rigorously assessed compared to chemotherapy for treating metastatic non-squamous and squamous NSCLC in patients with PD-L1 levels exceeding 1%.[18] Among patients with PD-L1 expression ≥50%, atezolizumab significantly improved OS, with a median OS of 20.2 months compared to 13.1 months in the chemotherapy group (HR = 0.59; 95% CI, 0.40–0.89; p = 0.0106).[18] Among patients with PD-L1 expression ≥ 1%, the significant difference in OS disappeared, reaching 17.5 months compared to 14.1 months (HR = 0.83; 95% CI, 0.65-2.07).[18]

The Impower 150 trial investigated the efficacy of the combination therapy of atezolizumab, bevacizumab, and chemotherapy (ABCP).[61] Regardless of PD-L1 levels, the ABCP therapeutic regimen offered substantial therapeutic benefits compared to the bevacizumab plus chemotherapy comparison group (BCP). Patients experienced an extended OS of 19.2 months in the ABCP group compared to 14.7 months in the BCP group (HR=0.78, 95% CI, 0.64–0.96; p = 0.02).[61] Furthermore, the ABCP combination therapy delivered a noteworthy enhancement in

PFS, with a duration of 8.3 months, compared to 6.8 months in the BCP group (HR=0.62, 95% CI, 0.52–0.74; $p < 0.001$).[61]

The Impower 130 trial assessed the efficacy of atezolizumab-chemotherapy versus chemotherapy alone in patients with metastatic non-squamous NSCLC.[26] Irrespective of the patients' PD-L1 expression levels, the atezolizumab-chemotherapy revealed a significant OS benefit, with 18.6 months in comparison to 13.9 months in the chemotherapy group (HR = 0.79; 95% CI, 0.64–0.98; $p = 0.033$).[26] Moreover, the atezolizumab-chemotherapy regimen significantly improved PFS, with a duration of 7.0 months versus 5.5 months in the chemotherapy group (HR = 0.64; 95% CI, 0.54–0.77; $p < 0.0001$).[26]

In the CheckMate 227 trial, patients with non-squamous or squamous NSCLC received nivolumab-ipilimumab or chemotherapy alone, regardless of their PD-L1 expression.[21] The combination therapy of nivolumab-ipilimumab exhibited a substantial improvement in OS, with a median OS of 17.1 months compared to 13.9 months for the chemotherapy group. For patients with PD-L1 expression of 1% or more, the OS was 17.1 months compared to 14.9 months ($p = 0.007$).[21] For patients with PD-L1 expression below 1%, the nivolumab-ipilimumab regimen also demonstrated an improved OS, with 17.2 months (95% CI, 12.8-22.0) compared to 12.2 months (95% CI, 9.2-14.3) for chemotherapy.[21]

Similarly, in the CheckMate 9LA trial, patients with non-squamous or squamous NSCLC received the combination therapy of nivolumab-ipilimumab-chemotherapy, or chemotherapy alone, irrespective of their PD-L1 expression.[25] The combination therapy demonstrated substantial efficacy, extending OS to 15.6 months compared to 10.9 months in the chemotherapy group (HR=0.72, 95% CI= 0.61-0.86).[25] Notably, this benefit persisted at the 2-year follow-up, with an impressive 2-year OS rate of 38% compared to 26% (chemotherapy alone). However,

nivolumab-ipilimumab-chemotherapy had a relatively higher incidence of AEs of grade ≥ 3compared to chemotherapy alone (25.4% vs.15.0%), indicating the importance of careful monitoring and management of treatment-related side effects.[25]

In the EMPOWER-Lung 1 trial, which compared cemiplimab to chemotherapy in patients with metastatic squamous or non-squamous NSCLC with PD-L1 expression of ≥50%, cemiplimab demonstrated significant improvements in both OS and PFS.[20] The median OS was not reached for the cemiplimab group, and was 14.2 months for chemotherapy (HR = 0.57, 95% CI, 0.42–0.77; p = 0.0002) [20]. Additionally, the cemiplimab group exhibited a longer median PFS of 8.2 months compared to 5.7 months in the chemotherapy group (HR = 0.54, 95% CI, 0.43–0.68, p < 0.0001).[20]

In the EMPOWER-Lung 3 trial, CCT was compared to chemotherapy alone in patients with advanced squamous or non-squamous NSCLC, regardless of PD-L1 expression.[24] CCT group exhibited a prolonged median OS of 22.9 months compared to 13.0 months in the chemotherapy-alone group (HR = 0.71; 95% CI, 0.53–0.93; P = 0.014).[24] Additionally, the combination therapy showed a significantly longer median PFS of 8.2 months compared to 5.0 months in the chemotherapy alone group (HR = 0.56; 95% CI, 0.44–0.70; P < 0.0001) [24]. However, it is important to note that the combination therapy was associated with a higher incidence of AEs grade ≥3 (43.6% vs. 32.4%).[24]

In summary, the **single agents of atezolizumab**, **pembrolizumab**, and **cemiplimab** demonstrate superior efficacy in survival compared to chemotherapy alone in the treatment of mNSCLC patients with PD-L1 expression ≥50%.[18-20] Furthermore, combination therapies such as **atezolizumab with chemotherapy**, **PCT**, and **CCT**, as well as **nivolumab-ipilimumab**, and **nivolumab-ipilimumab with chemotherapy**, all exhibit enhanced OS and PFS compared to

chemotherapy alone.[21-26] These findings underscore the significant therapeutic advancements offered by immunotherapies in improving outcomes for patients with mNSCLC.

Real-world evidence has provided more insight into the effectiveness of ICI treatments, which supplements clinical trial results.[62-64] Fujimoto et al. found that PCT had low real-world effectiveness for poor performance status patients compared to the clinical trial results.[62] According to lung cancer registry data from Central and Eastern European countries, the effectiveness of NSCLC immunotherapy is comparable to the efficacy observed in clinical trials.[64] Mahashabde et al. found that first-line use of ICIs was associated with improved 6-month survival outcomes than chemotherapy alone for NSCLC patients with brain metastases.[63]

Wang et al. conducted a network meta-analysis and found that the combination of chemotherapy and ICI significantly increased the objective response rate and PFS in NSCLC patients with high PD-L1 expression.[65] Dafni et al. also applied NMA and drew the same conclusion that adding chemotherapy to ICIs enhanced treatment efficacy as first-line treatment compared to ICI alone for advanced NSCLC patients, regardless of PD-L1 level.[66] One recently published real-world study found no significant difference in OS or PFS between ICI plus chemotherapy and ICI therapy alone for older adults with advanced NSCLC.[67] However, the unobserved survival benefits may be attributed to the relatively limited sample size and the real-world use of chemotherapy deviating from clinical trial protocols.[67] Besides that, the crossing Kaplan-Meier (KM) survival curves in this observational study raised concerns about the validity of the single HR in the CPH model to capture the time-varying treatment effectiveness.

Table 5. Phase 3 clinical trial results of the first-line ICI regimens for advanced/mNSCLC

Study	Comparison	Cancer Types	Patients Number	PD-L1 Levels	Results
KEYNOTE-024[19, 35, 36]	Pembrolizumab vs. Chemotherapy	Advanced non-squamous/Squamous	154 vs. 151	PD-L1 ≥ 50%	6-Month OS: 80.2% vs. 72.4% (HR = 0.60; 95% CI, 0.41–0.89; p = 0.005)
					PFS: 10.3 months vs. 6.0 months (HR = 0.50; 95% CI, 0.3–0.68; p < 0.001)
					Treatment-Related AEs Grade ≥ 3: 26.6% vs. 53.3%
	33 Months Results:	Advanced non-squamous/Squamous	154 vs. 151	PD-L1 ≥ 50%	OS: 30.0 months vs. 14.2 months (HR = 0.49; 95% CI, 0.34–0.69; p = 0.002)
					Treatment-Related AEs Grade ≥ 3: 32.2% vs. 53.3%
	Five Years Results:	Advanced non-squamous/Squamous	154 vs. 151	PD-L1 ≥ 50%	Median OS: 26.3 months vs. 13.4 months (HR = 0.62; 95% CI, 0.48- 0.81)
					5-Year OS Rate: 32.9% vs. 16.3%
KEYNOTE-042[34]	Pembrolizumab vs. Chemotherapy	Advanced non-squamous/Squamous	637 vs. 637	PD-L1 ≥ 1%	OS (PD-L1 ≥ 50%): 20.0 months vs. 12.2 months (HR = 0.69; 95% CI, 0.56–0.85; p = 0.0003)
					OS (1% ≤ PD-L1 < 50%): 13.4 months vs. 12.1 months (HR = 0.92; 95% CI, 0.77–2.11)
KEYNOTE-189[23]	Pembrolizumab + Chemotherapy vs. Chemotherapy	Metastatic non-squamous	445 vs. 171	Regardless of PD-L1 Expression	One-Year Survival Rate: 69.2% vs. 49.4% (HR = 0.49; 95% CI, 0.38–0.64)
					PFS: 8.8 months vs. 4.9 months (HR = 0.52; 95% CI, 0.43–0.64)
					AEs Grade ≥ 3: 67.2% vs. 65.8%
KEYNOTE-407[38]		Metastatic squamous	278 vs. 281		OS: 15.9 months vs. 12.3 months (HR = 0.64; 95% CI, 0.49–0.85)

	Pembrolizumab + Chemotherapy vs. Chemotherapy			Regardless of PD-L1 Expression	PFS: 6.4 months vs. 4.8 months (HR = 0.56; 95% CI, 0.45–0.701)
					AEs Grade ≥ 3: 69.8% vs. 68.2%
CheckMate 227[21]	Nivolumab + Ipilimumab vs. Chemotherapy	Non-squamous/Squamous	583 vs. 583	Regardless of PD-L1 Expression	OS (All Patients): 17.1 months vs. 13.9 months
					OS (PD-L1 ≥ 1%): 17.1 months vs. 14.9 months (p = 0.007)
					OS (PD-L1 ≤ 1%): 17.2 months vs. 12.2 months
CheckMate 9LA[25]	Nivolumab + Ipilimumab + Chemotherapy vs. Chemotherapy	Non-squamous/Squamous	361 vs. 358	Regardless of PD-L1 Expression	OS: 15.8 months vs. 12.0 months (HR=0.72, 95% CI= 0.61-0.86)
					2-Year OS Rate: 38% vs. 26%
					AEs Grade ≥ 3: 25.4% vs. 15%
IMpower 110[18]	Atezolizumab vs. Chemotherapy	Metastatic non-squamous/Squamous	277 vs. 277	PD-L1 ≥ 1%	PD-L1 ≥ 50% OS: 20.2 months vs. 13.1 months (HR = 0.59; 95% CI, 0.40–0.89; p = 0.0106)
					OS (Any PD-L1 Expression): 17.5 months vs. 14.1 months (HR=0.83; 95% CI, 0.65 to 2.07)
					AEs Grade ≥ 3: 30.1% vs. 52.5%
IMpower 150[61]	Atezolizumab + Bevacizumab + Chemotherapy vs. Bevacizumab + Chemotherapy	Metastatic non-squamous	356 vs. 336	Regardless of PD-L1 Expression	OS: 19.2 months vs. 14.7 months (HR = 0.78; 95% CI, 0.64–0.96; p = 0.02)
					PFS: 8.3 months vs. 6.8 months (HR = 0.62; 95% CI, 0.52–0.74; p < 0.001)
Mpower130[26]	Atezolizumab + Chemotherapy vs. Chemotherapy	Metastatic non-squamous	483 vs. 420	Regardless of PD-L1 Expression	OS: 18.6 months vs. 13.9 months (HR = 0.79; 95% CI, 0.64–0.98; p = 0.033)
					PFS: 7.0 months vs. 5.5 months (HR = 0.64; 95% CI, 0.54–0.77; p < 0.0001)

EMPOWER-Lung 1[20]	Cemiplimab vs chemotherapy	Metastatic squamous / non-squamous	283 vs. 280	PD-L1 ≥ 50%	OS: Not reached vs. 14.2 months (HR = 0.57, 95%CI, 0.42–0·77p=0.0002)
					PFS:8.2 months vs. 5.7 months (HR = 0.54,95%CI, 0.43–0.68, p<0.0001).
EMPOWER-Lung 3[24]	Cemiplimab + chemotherapy vs chemotherapy	Advanced squamous or non-squamous	312 vs. 154	Regardless of PD-L1 Expression	OS: 22.9 months vs. 13.0 months (HR = 0.71; 95% CI, 0.53–0.93; P = 0.014).
					PFS: 8.2 months vs. 5.0 months (HR = 0.56; 95% CI, 0.44–0.70; P < 0.0001).
					Grade ≥3 AEs 43.6% vs. 32.4%

ICI: immune checkpoint inhibitor; PD-L1: programmed cell death ligand 1; OS: overall survival; HR: hazard ratio; PFS: progression-free survival; AEs: adverse events

2.4. Immune-related adverse events in immunotherapy

2.4.1. Incidence and common irAEs in patients with mNSCLC

Immunotherapy has significantly improved the survival outcomes for NSCLC patients. However, the distinctive mechanism of immunotherapy that exerts anti-tumor effects also determines its unique toxicity profiles. The AEs that occur after and as a consequence of immunotherapy are called irAEs.[46] A meta-analysis conducted by Wang et al. in 2017 found that the overall incidence of irAEs in all malignancies was 26.82%, with 6.10% for severe irAEs. The incidence of death due to irAEs was around 0.17%.[68] IrAEs commonly present in the gastrointestinal tract, endocrine glands, skin, and liver. Common irAEs include skin rashes, colitis, hepatitis, pneumonitis, and thyroid dysfunction, among others.[69]

The incidence of irAEs is variably reported by different studies. The reported incidence of any grade irAEs ranged from 30% to 49% in cancer patients treated with ICIs.[11-13] The spectrum of irAEs also differs across ICI treatments. For instance, in patients with NSCLC, the most common irAEs associated with nivolumab are rash and diarrhea, and those associated with pembrolizumab are thyroid toxicities.[13]

2.4.2. Management of irAEs among patients with mNSCLC

Effectively managing irAEs in patients with NSCLC receiving immunotherapy is a crucial aspect of patient care. Several systematic reviews have outlined how to address these irAEs effectively depending on different complications and toxicity grades.[70, 71] Table 6 summarizes the guidelines of irAEs management for mNSCLC patients after ICI treatment.[70-72]

Table 6. Guidelines of irAEs management for mNSCLC patients after ICI treatments

Corticosteroids as Primary Treatment	Corticosteroids are recommended as the primary treatment for most irAEs associated with ICIs as they help suppress the immune system to mitigate AEs.	
Management Based on Toxicity Grades	**Grade 1 Toxicities**	In most cases, patients are recommended to continue ICI therapy with close monitoring. However, exceptions exist for specific severe toxicities involving the blood, heart, or nervous system.
	Grade 2 Toxicities	Consider suspending ICI therapy and resuming it when symptoms regress to grade 1 or lower, corticosteroids may be administered if symptoms persist for more than one week. In most cases, patients are recommended to continue ICI therapy with close monitoring. However, exceptions exist for specific severe toxicities involving the blood, heart, or nervous system.
	Grade 3 Toxicities	If a patient experiences Grade 3 toxicities, the ICI administration should be stopped, and high-dose corticosteroids should be initiated. The use of corticosteroids should be gradually reduced over a period of 4 to 6 weeks, or 6 to 8 weeks in case of irAEs such as pneumonitis or hepatitis. If the patient's condition does not improve within 48 to 72 hours, additional immunosuppressive therapies may be necessary. Rechallenging with ICIs can be considered once toxicities reduce to grade 2.

	Grade 4 Toxicities	For Grade 4 toxicities, ICIs should be permanently discontinued, except for endocrinopathies that are controlled with hormone replacement therapy.
Prophylaxis and Precautions	Various prophylactic measures are recommended to prevent microbial infections, gastritis, bone loss, and conditions like pneumocystis pneumonia. These measures include proton pump inhibitors or histamine H2 blockers, vitamin D and calcium supplements, and prophylaxis.	
Screening before Initiating Tumor Necrosis Factor Inhibition	Testing for hepatitis B and C, as well as latent/active tuberculosis, is recommended before initiating TNF inhibition (e.g., infliximab) due to the risk of reactivation.	

2.5. Predictive models that have been developed to predict irAEs

ML in cancer treatment analytics has recently gained popularity. AI-based techniques can analyze large amounts of data to predict healthcare outcomes, including irAEs. Iivanainen et al. (2021) used ML to model electronic patient-reported outcomes (ePROs) to forecast irAEs for lung cancer patients.[28] The research showed that if ICI-treated cancer patients reported symptoms like diarrhea and pain in the joints, especially with a higher level of severity, it often indicates the presence of irAEs. On the other hand, the model identified fever, chest pain, and stomach pain as the main symptoms that predict the potential irAEs.[28]

Gong et al. (2023) used hospital electronic medical records to identify and predict ICI-related pneumonitis (IRP) based on ML method.[27] This study leveraged the Elastic Net model for IRP prediction and a repeated k-fold cross-validation framework for model validation.[27] The final predictive model consisted of 11 predictors, including sindilizumab, tirelizumab, NSCLC, ≥2 underlying diseases, history of lung diseases, percentage of CD4+ lymphocytes, body temperature, KPS score ≤ 70, hemoglobin, metastatic stage, and history of antitumor therapy.[27]

Even though several predictive models were developed for irAEs after immunotherapy, some key covariates are not considered, including patients' demographics, comorbidities, and different ICI regimens. [27, 28] Besides that, the existing predictive models were limited to either small sample sizes or did not specifically focus on mNSCLC, which limited the model's implications to mNSCLC patients.[27, 28]

2.6. Cost-effectiveness of the combination therapy of ICIs in mNSCLC

In cost-effective analyses evaluating ICI treatment for mNSCLC patients, outcomes vary based on different model inputs for survival, cost, AE rates, and disease utility. Despite discrepancies

across studies, current synthesized evidence suggests that atezolizumab-monotherapy, ABCP, and tremelimumab-durvalumab are not cost-effective compared to chemotherapy alone.[73, 74] Pembrolizumab-monotherapy, PCT, nivolumab-ipilimumab, nivolumab-ipilimumab-chemotherapy, cemiplimab-monotherapy, and CCT were assumed to be cost-effective compared to chemotherapy in some studies.[73, 75-77] Yang et al. (2023) evaluated the cost-effectiveness of ICIs marketed before 2021(including pembrolizumab, atezolizumab, nivolumab, and ipilimumab). The results showed that first-line pembrolizumab, PCT, and nivolumab-ipilimumab were the preferred strategies for patients with PD-L1 ≥ 50%, ≥1% and ≤49%, < 1%, respectively.[78] Regarding the latest marked ICI, cemiplimab monotherapy is preferred over pembrolizumab monotherapy for patients with PD-L1 ≥ 50%.[79, 80] Table 7 comprehensively overviews various cost-effective evaluations for ICI combination therapies and shows the variety of results.

Ralph et al. (2018) compared the cost-effectiveness of PCT versus chemotherapy for metastatic non-squamous NSCLC patients from a U.S. third-party healthcare payer perspective.[75] The results reported that the incremental cost-effectiveness ratios (ICERs) are $87,242/life year and $104,823/quality-adjusted life year (QALY) for PCT compared to chemotherapy alone. Stratifying by the PD-L1 expression level, the corresponding ICERs per QALY are $103,402, $66,837, and $183,529 for PD-L1 ≥ 50%, 1–49%, and <1% groups, respectively. The findings suggested PCT were cost-effective with ICERs below three times the U.S. per capita GDP threshold of $195,000/QALY.[75]

Zeng et al. (2019) from a U.S. payer perspective showed PCT provided an additional 0.78 QALYs at an incremental cost of $151,409 for metastatic non-squamous NSCLC patients, with

an ICER of $194,372/QALY.[77] ICER for PCT was >$149 680/QALY in all of the univariable and probabilistic sensitivity analyses.[77]

The divergence between the two studies is that the first study combined the SEER cancer mortality rate to extrapolate the survival beyond the trial periods.[75] Using both clinical trials data and SEER data, the first study simulated more accurate survival compared to prolonging the KM curve using clinical trials data alone. The PCT combination treatment strategy is likely to be cost-effective for non-squamous NSCLC patients if the threshold is $195,000/QALY. [75]

Based on the existing studies, atezolizumab combination therapies would not be a cost-effective choice compared to either PCT or chemotherapy alone.[81, 82] Criss et al. (2019) assessed ABCP in the first-line mNSCLC treatment from the U.S. health care perspective. The study revealed an estimated ICER of $201,676 per QALY compared to BCP. [81] PCT dominated ABCP, resulting in an ICER of $116,698 per QALY compared to BCP. ABCP was not considered cost-effective at a willingness-to-pay threshold of $100,000 per QALY.[81]

Another study (Ding et al. 2020) from the U.S. payers' perspective compared atezolizumab-chemotherapy to chemotherapy alone, showing an increase of 0.16 QALYs with an additional cost of $109,809, resulting in an ICER of $670,310 per QALY.[82] The study concluded that first-line treatment with ACP was not a cost-effective option for patients with metastatic non-squamous NSCLC, as the ICER remained consistently greater than $150,000/QALY across all PD-L1 levels subgroups.[82]

Nivolumab-ipilimumab (sometimes plus chemotherapy) could also be a cost-effective choice compared to chemotherapy alone.[76, 83] A recent study (Polyzoi et al. 2022) conducted from the U.S. healthcare payer perspective revealed that the nivolumab-ipilimumab with two cycles of platinum-doublet chemotherapy is associated with significantly higher health benefits

compared to chemotherapy alone.[76] The study found that the combination resulted in an increase in life years (Lys) (3.71 vs. 2.89) and QALYs (2.86 vs. 2.37), and higher costs ($317,581 vs $119,909) with an ICER of $132,960/QALY gained for advanced NSCLC patients. The probability of nivolumab-ipilimumab-chemotherapy being cost-effective ranged from 78% to 100% at a willingness-to-pay threshold of $150,000–$250,000/QALY.[76]

Hao et al. (2021) conducted analyses from the perspective of the U.S. third-party payer, revealing that nivolumab-ipilimumab led to an increase of 2.260 QALYs at an additional cost of $95,617 compared to chemotherapy.[83] This resulted in an ICER of $75,871 per QALY gained. Sensitivity analysis indicated that the treatment of nivolumab-ipilimumab had a 99% chance of being cost-effective, with respect to the ICER threshold of $100,000/QALY across all PD-L1 subgroups.[83]

Liang et al. (2023) evaluated the cost-effectiveness of CCT as first-line treatment compared to chemotherapy alone from a U.S. third-party payer perspective. The study showed CCT for advanced NSCLC increased 0.237 QALYs with $50,796 additional cost, leading to an ICER of $214,256/QALY gained.[84] However, Zhu et al. (2023) used updated 2-year survival information of first-line CCT in the EMPOWER-Lung 3 clinical trial. They found the ICER reduced to $68,644/QALY compared to chemotherapy alone from the same perspective.[44] Two studies draw different conclusions on whether CCT is cost-effective compared to chemotherapy, primarily due to differences in follow-up duration.[44, 84]

Both PCT and CCT are potential cost-effective choices compared to chemotherapy alone. However, the comparison between the newly approved regimen (CCT) and the standard-care immunotherapy regimen (PCT) has not been conducted. Moreover, based on a network meta-analysis of clinical trial data, PCT showed superior survival outcomes compared to CCT for

metastatic non-squamous NSCLC patients.[33] The cost-effectiveness of CCT also needs to be further evaluated after stratifying by different histologies.

Table 7. Cost-effectiveness of first-line ICI combination therapies

Author	Comparator	Indications	Perspective (US)	ICER ($/QALY)	Cost-effective
Ralph et al. (2018)	PCT versus chemotherapy	metastatic non-squamous NSCLC	third-party healthcare payer	104,823	Yes
Zeng et al. (2019)	PCT versus chemotherapy	metastatic non-squamous NSCLC patients	payer	194,372	No
Criss et al. (2019)	atezolizumab in combination with bevacizumab and chemotherapy versus bevacizumab and chemotherapy	metastatic non-squamous NSCLC	healthcare	201,676	No
Ding et al. (2020)	atezolizumab-chemotherapy to chemotherapy	metastatic non-squamous NSCLC	payers	670,309	No
Polyzoi et al. (2022)	Nivolumab-ipilimumab plus chemotherapy versus chemotherapy	advanced NSCLC	healthcare payer	132,960	Yes
Hao et al. (2021)	Nivolumab-ipilimumab versus chemotherapy	advanced NSCLC	third-party payer	75,871	Yes
Liang et al. (2023)	CCT versus chemotherapy	advanced NSCLC	third-party payer	214,256	No
Zhu et al. (2023)	CCT versus chemotherapy	advanced NSCLC	healthcare system	68,644	Yes

NSCLC: non-small cell lung cancer; ICER: incremental Cost-Effectiveness ratio; QALY: quality-adjusted life-year

2.7. Summary of current knowledge gaps in immunotherapy for mNSCLC

2.7.1. Current knowledge gaps

2.7.1.1. Effectiveness of ICIs

The FDA's approval of ICI treatment regimens is based on their superior efficacy compared to chemotherapy alone, as demonstrated in clinical trials.[17-26, 45] Existing real-world evaluations only provided descriptive results, failed to distinguish different ICIs, or did not have a comparison group.[62-64] The most effective immunotherapy for achieving optimal long-term survival benefits remains unclear, due to the absence of head-to-head trials and longitudinal studies. Besides that, there is no clinical trial to examine the efficacy of ICI-Chemotherapy compared to ICI-Monotherapy. The optimal use of chemotherapy in combination with ICIs also remains unclear.

2.7.1.2. Prediction of irAEs after ICI treatments

IrAEs pose an increased risk of morbidity, discontinuation of treatment, and even death in rare cases.[46] Existing ML prediction models for irAEs either have not explicitly focused on mNSCLC, are restrained by small sample sizes, or fail to incorporate key predictive features such as patients' demographics, comorbidities, different ICI regimens, and time to treatments.[27, 28] The limitation of predictive models restricted the applicability to mNSCLC patients. Further

studies are warranted to address these gaps and develop more tailored predictive models for irAEs in this population.

2.7.1.3. Cost-effectiveness of ICIs

Assessing the cost-effectiveness of ICIs is crucial for treatment decision-making for patients and healthcare systems. Among existing ICI treatment regimens, PCT was considered the preferred first-line treatment for patients regardless of PD-L1 level, from a cost-effective perspective, prior to the approval of cemiplimab.[16] Clinical trials have demonstrated that CCT exhibits superior survival outcomes compared to chemotherapy alone.[20, 37] However, whether CCT is a cost-effective choice compared to PCT remains unknown and requires further investigation.

2.7.2 Proposed dissertation study to address these knowledge gaps

The goal of this dissertation is to provide new, real-world evidence on the effectiveness, safety, and cost-effectiveness of ICIs for patients with mNSCLC**.** The 2014-2020 SEER-Medicare lung cancer data was used for Aim 1 and Aim 2, as it provides detailed information on patients with Medicare beneficiaries. Multiple approaches (i.e., new user cohort, target trial emulation, ML, and cost-effectiveness analysis) were employed to improve the quality of evidence. Aim 3 used data from clinical trials, CMS drug price lists, and published literature. There are three aims we propose:

Aim 1. To compare the effectiveness of individual ICIs and of ICI–Chemotherapy versus ICI-Monotherapy as first-line treatment in patients with mNSCLC.

Aim 1 leveraged large-scale, cancer registry-claims-linked data to provide the first head-to-head comparisons of three individual ICI treatment regimens (pembrolizumab, atezolizumab, and nivolumab) in survival outcomes. OS was compared between patients receiving first-line ICI-Chemotherapy and those receiving first-line ICI-Monotherapy.

Aim 2. To develop machine learning models for the prediction of irAEs after ICI initiation among patients with mNSCLC.

LASSO and three ML algorithms approaches were employed and compared to enhance model prediction performance in predicting 3-month irAEs after ICI initiation among patients with mNSCLC.

Aim 3. To compare the cost-effectiveness of first-line cemiplimab plus chemotherapy with pembrolizumab plus chemotherapy for mNSCLC patients.

Aim 3 developed a partitioned survival model to estimate the cost-effectiveness of CCT as the first-line treatment for patients with mNSCLC compared to PCT.[20, 33] The partitioned survival model was designed from PFS to PD and ultimately to death. The analysis evaluated total costs, QALYs for both treatment strategies, and the ICER between the two regimens.

Chapter 3: Methods

3.1. Description of the study

This dissertation project evaluated the effectiveness, safety, and cost-effectiveness of ICIs in mNSCLC. Aim 1 leveraged the SEER-Medicare data to provide the first head-to-head comparisons of survival outcomes among three individual ICI treatment agents (pembrolizumab, atezolizumab, and nivolumab), and between ICI-Chemotherapy and ICI-Monotherapy. Aim 2 developed and tested LASSO and ML models to predict the risk of irAEs in mNSCLC patients within three months after ICI initiation. Aim 3 assessed the cost-effectiveness of the recently marketed first-line CCT compared to PCT for patients with mNSCLC.[33]

3.2. Aim 1: To compare the effectiveness of individual ICIs and of ICI–Chemotherapy versus ICI-Monotherapy as first-line treatment in patients with mNSCLC.

3.2.1. Comparison of ICI agents

3.2.1.1. Research questions

What is the most effective first-line ICI treatment among pembrolizumab, atezolizumab, and nivolumab regarding survival outcomes for patients with mNSCLC?

3.2.1.2. Study design

We conducted a retrospective new user cohort study to compare three marketed ICIs (pembrolizumab, atezolizumab, and nivolumab) using the 2014-2020 SEER-Medicare data.[85]

3.2.1.3. Data sources

This study used the SEER cancer registry data from January 2015 to December 2019. The SEER dataset was linked to the Medicare enrollment claims data from January 2015 to December 2020. The SEER-Medicare data represents the linkage of two expansive population-based data sources. It provides detailed insights into patients with cancer who are Medicare beneficiaries.[85] SEER serves as the most extensive data repository for cancer research, covering 48% of U.S. cancer patients.[86] It collects and publishes data on patient demographics, primary tumor site, tumor characteristics, the initial treatment cause, and subsequent follow-ups. Medicare claims offer comprehensive health coverage for adults aged 65 and older, as well as for individuals under 65 who receive Social Security Disability Insurance or have end-stage renal disease. The linkage of these two data sources creates a unique population-based information pool that can be used for an array of epidemiological studies (i.e., treatment patterns).[87]

3.2.1.4. Study Sample

The study included patients diagnosed with mNSCLC between January 1, 2015, and December 31, 2019, treated with first-line ICIs alone or combined with chemotherapy. MNSCLC patients

were identified using the International Classification of Diseases for Oncology, third edition (ICD-O-3) codes from the SEER database (C340-C343, C348-C349) with the histology codes (Table 8).[88-91] The inclusion criteria were (1) aged 66 years or older at the time of mNSCLC diagnosis, (2) initiated first-line pembrolizumab, nivolumab, or atezolizumab in six months after mNSCLC diagnosis, and (3) continuously enrolled in Medicare Part A and Part B from six months before diagnosis to the initiation of ICI treatments. Pembrolizumab, nivolumab, and atezolizumab were identified from Medicare Part B claims using Healthcare Common Procedural Coding System codes (HCPCS). First-line treatments were defined as the initial anticancer therapies after diagnosis. Given that one cycle of first-line treatment typically spans 21 days, patients who initiated chemotherapy or radiation after diagnosis but received immunotherapy within a 21-day window following chemotherapy or radiation were also classified as receiving first-line ICI treatments (Figure 1).[34, 63] The exclusion criteria were beneficiaries who (1) received ICIs, chemotherapy, and radiation six months before cancer diagnosis and (2) initiated ICI treatment after six months of diagnosis. Chemotherapy and radiation were identified using HCPCS codes and ICD-9/10 codes (Table 9).[92]

Table 8. ICD-O-3 codes for mNSCLC patients classified by histologic subtype

Lung cancer ICD-O-3	C340-C343,C348-C349	
Histology ICD-O-3	Squamous	8010/3, 8012/3, 8020/3, 8046/3, 8050/3, 8051/3, 8140/3, 8141/3, 8143/3, 8147/3, 8250-8255/3, 8260/3, 8310/3,8430/3, 8480/3, 8481/3, 8490/3, 8560/3, and 8571-8575/3
	Non-squamous	8052/3, 8070-8083/3, 8570/3

Figure 1. New user cohort design of mNSCLC patients treated with first-line ICIs

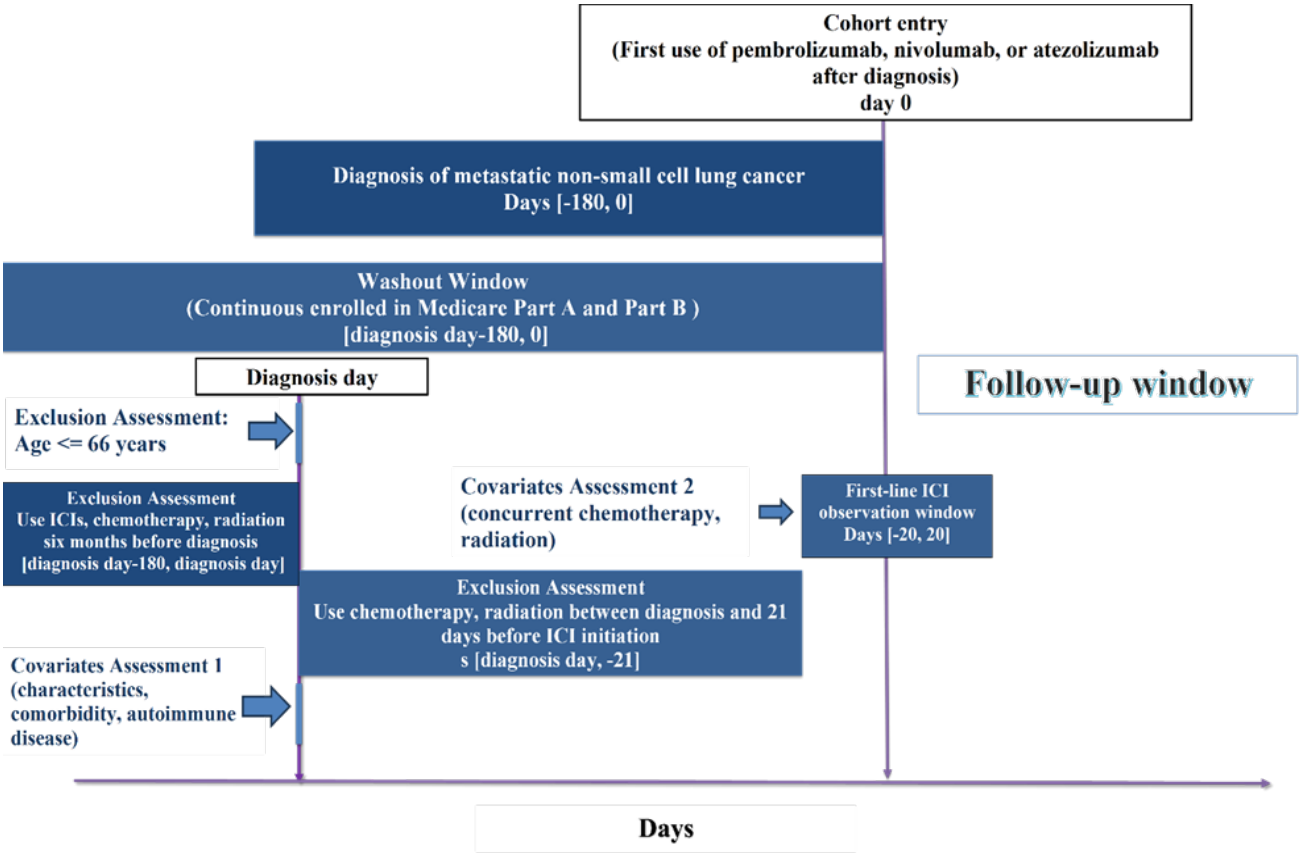


Table 9. Medical code for ICI, chemotherapy, radiation, and targeted therapy

ICI HCPCS	Atezolizumab	J9022, C9483
	Nivolumab	J9299, C9453
	Pembrolizumab	J9271, C9027
	Ipilimumab	J9228, C9284
	Durvalumab	J9173, C9492
	Cemiplimab	J9119
Chemotherapy ICD-9, ICD-10	ICD9	Diagnostic: V58.1, Procedure:99.25
	ICD10	Diagnostic: Z51.11, Procedure: 3E03305, 3E04305, XW03351, XW033B3, XW033C3, XW04351, XW043B3, XW043C3
Chemotherapy HCPCS	Carboplatin	J9045
	Cisplatin	C9418, J9060, J9062
	Docetaxel	J9170, J9171
	Paclitaxel	C9127, C9431, J9265, J9267, J9264
	Pemetrexed	C9213, J9304, J9305
	Gemcitabine	J9201, J9198
	Other HCPCS codes related to the chemotherapy*	96400, 96401, 96402, 96405, 96406, 96408, 96409, 96410, 96411, 96412, 96413, 96414, 96415, 96416, 96417, 96420, 96422, 96423, 96425, 96440, 96445, 96446, 96450, 96499, 96520, 96521, 96522, 96523, 96530, 96542, 96545, 96549, Q0083,Q0084, Q0085, Q2017, Q2024, S0087, S0088
Radiation	ICD-9codes	Diagnostic: V58.0, V66.1, V67.1, Procedure: 92.2, 92.20-92.29, 92.3, 92.30-92.33, 92.39, 92.4, 92.40, 92.41
	ICD-10 codes	Diagnostic: Z510, Procedure: 0HHT01Z, 0HHT31Z, 0HHT71Z, 0HHT81Z, 0HHTX1Z, 0HHU01Z, 0HHU31Z, 0HHU71Z, 0HHU81Z, 0HHUX1Z, 0HHV01Z, 0HHV31Z, 0HHV71Z, 0HHV81Z, 0HHVX1Z, 0HHW01Z, 0HHW31Z, 0HHW71Z, 0HHW81Z, 0HHWX1Z, 0HHX01Z, 0HHX31Z, 0HHX71Z, 0HHX81Z, 0HHXX1Z
	HCPCS	HCPCS/CPT: 76370, 76950, 76965, 77261-77263, 77280, 77285, 77290, 77293, 77295, 77299-77301, 77305-77307, 77310, 77315-77318, 77321, 77326-77328, 77331-77334, 77336, 77338, 77370-77373, 77385-77387, 77399, 77401-77404, 77406-77409, 77411-77414, 77416-77418, 77421-77425, 77427, 77431, 77432, 77435, 77469, 77470, 77499, 77520, 77522, 77523, 77525, 77750, 77761-77763, 77767, 77768, 77770, 77771, 77772, 77776-77778, 77781-77790, 77799, 0182T, C1325, C1348, C1350, C1700- C1712, C1715-C1720, C1728, C1790-

		C1806, C2616, C2632, C2633, C9120, C9216, C9430, C9714, C9715, G0174, G0178, G0179, G0251, G0256, G0261, G0273, G0274, G0338-G0340, J0128, J1675, J1950, J3315, J9165, J9202, J9217-J9219, J9225, J9226, Q2020, S0165, S0175, S0189, S9560

MNSCLC: metastatic non-small cell lung cancer; ICI: immune checkpoint inhibitor; HCPCS: Healthcare Common Procedure Coding System; ICD-9: International Classification of Diseases Nine Version; ICD-10: International Classification of Diseases Ten Version; NDC: National Drug Code

*These codes are used in washout cleaning but not for first-line treatment identification.

3.2.1.5. Survival Outcome

The primary outcome is OS, defined as the time (in days) from the initiation of first-line ICI treatment to death. Observations with disenrollment from Medicare Part A or Part B, or those that reached the end of data availability, were treated as censored at that time.

3.2.1.6. Covariates

The covariates included (1) patients' demographic characteristics (age, sex, race, metropolitan status, geographic region, and socioeconomic status as identified by the Yost index in SEER data. Yost index reflected an individual's economic, social, and educational standing), (2) histology of NSCLC (squamous and nonsquamous), (3) other first-line cancer treatments (chemotherapy, radiation), (4) modified Charlson comorbidity index (CCI), (5) autoimmune disease history, and (6) time from cancer diagnosis to treatment initiation (in days). Patients' characteristics and cancer histology were identified at the time of diagnosis. Autoimmune disease history was defined as the presence of systemic immune-mediated disorders involving multiple organ systems (Table 10).[93] The modified CCI (excluding cancer) and autoimmune disease history were measured using Medicare claims data within 6 months before cancer diagnosis.[94] The identification of the new user cohort and baseline covariates is illustrated in Figure 1.

Table 10. Autoimmune disease and ICD-9-CM/ICD-10-CM codes

Organ system	ICD-9 codes	ICD-10 codes
Dermatologic	693.0 698.8 697.0 709.00, 709.01, 709.09 694.5 695.13, 695.14	L27.0, L27.1 L29.8, L29.9 L43.x, L44.3, L66.1 L80, L81.8, L81.9 L12.0 L51.1, L51.3
Hematologic	285.3, 285.8, 285.9284.x, 283.x 287.3, 287.31, 287.8, 287.9, 287.31, 287.32, 287.4, 287.49, 287.5287.8, 287.9 288.00, 288.03, 288.09 288.4, 288.5x, 288.8, 288.9	D59.x, D61.x, D60.x, D64.2, D64.3, D64.8 D69.3, D69.41, D69.49, D69.59, D69.6 D72.1, D72.81, D72.810, D72.818, D72.819, D70.9, D70.4, D70.2, D76.1, D76.3
Pulmonary	508.8, 508.9, 486.x, 516.3x, 516.9	J84.11x, J70.9, J70.8, J70.2, J70.3, J70.4, J18.9, J84.89, J84.9
Liver	573.3, 790.5	K71, R74.8, K75.4, K75.9, R94.5
Gastrointestinal	558.2, 558.3, 558.4, 558.9, 555, 556.8, 556.9 577.0 528.x	K52.1, K52.29, K52.3, K52.9, K52.89, K53.82 K85.x K12.30, K12.31
Endocrine	244.3, 244.8, 244.9 242.x 250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93 250.11, 250.13 253.8 255.41	E03.2, E03.8, E03.9 E05.x E09.x, E10.x, E13 E10.1 E23.6 E27.1, E27.3, E27.4
Renal	584.x 591.10, 591.11, 583.89 580.x, 581.x, 583.x	N17.x N10.x, N12.x, N14.1, N14.2 N00.x, N01.x, N04.x, N05.x N06.x,
Cardiac	427.x 410.x 422.x, 429.x 420.x, 423.x 425.4, 425.9	I48.x, I47.x, I49.x, I46.x I21.x I40.x, I51.4, I51.8, I51.9 I30.x I31.4, I31.8-9 I42.0, I42.7, I42.9

Musculoskeletal	710.3, 710.4 714.x 729.1 725, 446.5 729.2	M33 M05, M06, M08.0, M08.2, M08.3, M08.4, M08.8, M08.9, M12.0 M79.1 M35.5, M31.5, M31.6 M79.2
Central Nervous System (CNS)	047.9, 322.9 323.8, 323.81, 323.82, 323.7, 323.71, 323.72, 323.9 357.0 358.0 357.89	G03.9, A87.9 G92, G04.81, G04.89, G04.90, G04.91 G61.0 G70.0 G64

3.2.1.7. Statistical analysis

The survival curves were generated using the KM method, and treatment groups were compared using log-rank tests. OS was compared by unadjusted univariable, multivariable-adjusted, and PSM CPH models. The assumption of the hazard function under the CPH model and the calculation of HR are shown below:

$$h(t) = h_0(t) \times \exp(\beta^T x)$$

$$Hazard\ Ratio = \left(\frac{h(t|x_1)}{h(t|x_2)}\right) = \exp(\beta^T x_1 - \beta^T x_2)$$

t: survival time, h(t): hazard function, β: coefficients of covariates, $h_0(t)$: baseline hazard

In the PSM method, we used multivariable logistic regression to determine the propensity score (PS) of receiving one ICI over another ICI based on all the covariates mentioned above. Patients were matched based on the nearest neighbor of estimated PS, with matching ratios of 1:5 for atezolizumab/nivolumab vs. pembrolizumab, and 1:1 for atezolizumab vs. nivolumab. This matching process aims to balance the distribution of measured confounders between groups, thereby mimicking the randomization in clinical trials and reducing bias in the estimated treatment effect. Post-matching covariate balance was assessed using standardized mean differences (SMD). We fitted the CPH models among the matched treatment groups, with the treatment group as the primary exposure and any covariates that remained unbalanced after matching (SMD > 0.1) as additional model terms.[95]

To evaluate the treatment's effectiveness among adherent patients and minimize confounding from ICI treatment switching, we conducted a sensitivity analysis by applying two conditions: including only patients who continuously used ICIs for at least three months after initiation and

censoring patients upon switching to another ICI. We also conducted subgroup analyses to identify variations in treatment effectiveness for different histology patients and ICI regimens. Specifically, we performed subgroup analyses for patients with nonsquamous or squamous histology and for those receiving ICI-Monotherapy or ICI-Chemotherapy.

The proportional hazards (PH) assumption for each model was assessed using the Schoenfeld residual test, along with visual inspection of residual plots and KM curves.[96] In the multivariable models, the PH assumption was evaluated for each covariate. For categorical variables that violated this assumption, we employed a stratified Cox proportional hazards model. Each stratum was assigned its own baseline hazard function, enabling variation in hazard rates across strata while maintaining the consistency of covariate effects across all strata. For continuous variables that violated the assumption, we incorporated time-varying coefficients to account for their non-proportional effects over time.[97]

If the global PH assumption was violated, even after stratifying and adjusting for covariates, we would use the Restricted Mean Survival Time (RMST) method. RMST compared the average survival time over a specified period, without having to assume PH.[98] We applied univariable, multivariable, and PSM RMST models, calculating RMST ratios to comprehensively assess treatment effects.[99]

3.2.2. Comparison of ICI regimens

3.2.2.1. Research questions

Is there a survival benefit of adding chemotherapy to ICI regimens compared to ICIs alone for patients with mNSCLC?

Does extending chemotherapy from 4 to 6 cycles improve survival in patients receiving first-line ICI-Chemotherapy?

3.2.2.2. Emulating target trials in the SEER-Medicare linked database

Our approach involved two key steps. First, we specified the protocol for two hypothetical target trials: (1) first-line ICI-Monotherapy vs. ICI-Chemotherapy, and (2) 4 vs. 6 cycles of chemotherapy among patients receiving ICI-Chemotherapy. The hypothetical target trials were designed based on existing randomized trials, real-world evidence of treatment utilization, and oncology clinician's views.[100-103] Second, we emulated target trials using the SEER-Medicare data. The specifications of the target trials and the emulation procedure are summarized in Table 11 and Table 12.

Table 11. Protocol of the target trial to evaluate the addition of chemotherapy to first-line immunotherapy in metastatic non-small cell lung cancer and emulation procedure using the SEER-Medicare database

Protocol Component	Description of Target Trial	Emulation Using SEER-Medicare Data
Eligibility	• Diagnosis of mNSCLC between Jan 01, 2015, and Dec 31, 2019 • Aged 66 or older at diagnosis, continuously enrolled in Medicare Parts A and B six months prior to diagnosis through the initiation of first-line treatment • Initiation of first-line ICI-Monotherapy or ICI-Chemotherapy within 6 months of diagnosis • No prior ICI, chemotherapy, or radiation treatment six months before diagnosis	Same as the target trial.
Treatment Strategies	• First-line ICI-Chemotherapy with continuous use of chemotherapy for at least four cycles • First-line ICI-Monotherapy	Same as the target trial.
Assignment Procedures	Participants were randomized to receive either ICI-Chemotherapy or ICI monotherapy	Randomization was assumed conditional on baseline covariates: age, sex, race, metropolitan status, geographic region, socioeconomic status, year of diagnosis, histology, first-line radiation, time from diagnosis to the treatment initiation,

		adjusted CCI[#], pre-treatment emergency department visits*, pneumonitis*, diarrhea*, hypothyroidism*, and acute kidney injury*.
Follow-up	Follow-up begins at the initiation of first-line treatment and ends at the earliest of death, loss of insurance eligibility, December 31, 2020, or 72 weeks	Same as the target trial
Outcome	Death confirmed by National Death Index in Medicare claims	Same as the target trial
Causal Contrast	Intention-to-treat effect, per-protocol effect	Modified intention-to-treat effect: the effect of ICI-Chemotherapy initiation vs ICI-Monotherapy initiation, per-protocol effect
Analysis Plan	Intention-to-treat analysis; Per-protocol analysis: Stabilized IPCW with censoring at deviation from protocol. Weights are estimated as a function of baseline and time-varying covariates. Time-varying covariates included emergency department visits, ICI utilization, CCI, pneumonitis, diarrhea, hypothyroidism, and acute kidney injury	Same as the target trial

IPCW: Inverse probability censor weight, CCI: Charlson comorbidity index
Identification based on six months before first-line ICI initiation (Index date)
* Identification based on the 21 days before the Index date

Table 12. Protocol of the target trial to evaluate the 4 vs 6 cycles of chemotherapy in metastatic non-small cell lung cancer and emulation procedure using the SEER-Medicare database

Protocol Component	Description of Target Trial	Emulation Using SEER-Medicare Data
Eligibility	• Diagnosis of mNSCLC between Jan 01, 2015, and Dec 31, 2019 • Aged 66 or older at diagnosis, continuously enrolled in Medicare Parts A and B six months prior to diagnosis through the initiation of first-line treatment • Initiation of first-line ICI-Chemotherapy within 6 months of diagnosis • No prior ICI, chemotherapy, or radiation treatment six months before diagnosis • Received 4 cycles of chemotherapy after ICI-Chemotherapy initiation	Same as the target trial.
Treatment Strategies	• Four cycles of chemotherapy in ICI-Chemotherapy regimens • Six or more cycles of chemotherapy in ICI-Chemotherapy regimens	Same as the target trial.
Assignment Procedures	Participants were randomized to receive either 4 cycles of chemotherapy or 6 or more cycles of chemotherapy	Randomization was assumed conditional on baseline covariates: age, sex, race, metropolitan status, geographic region, socioeconomic status, year of diagnosis, histology, first-line

		radiation, time from diagnosis to the treatment initiation, adjusted CCI[#], pre-treatment emergency department visits*, pneumonitis*, diarrhea*, hypothyroidism*, and acute kidney injury*, ICI utilization at four-cycle*.
Follow-up	Follow-up begins at the initiation of first-line treatment and ends at the earliest of death, loss of insurance eligibility, December 31, 2020, or 72 weeks	Same as the target trial
Outcome	Death confirmed by National Death Index in Medicare claims	Same as the target trial
Causal Contrast	Per-protocol effect	Same as the target trial
Analysis Plan	Intention-to-treat analysis; Per-protocol analysis: Stabilized IPCW with censoring at deviation from protocol. Weights are estimated as a function of baseline and time-varying covariates. Time-varying covariates included emergency department visits, ICI utilization, CCI, pneumonitis, diarrhea, hypothyroidism, and acute kidney injury.	Same as the target trial

IPCW: Inverse probability censor weight, CCI: Charlson comorbidity index
Identification based on six months before first-line ICI initiation (Index date)
* Identification based on the 21 days before the Index date

3.2.2.3. Eligibility Criteria

This study included patients diagnosed with mNSCLC between January 1, 2015, and December 31, 2019, treated with first-line ICI-Monotherapy or ICI-Chemotherapy. The ICD-O-3 codes were used to identify patients with mNSCLC in the SEER database (Table 8).[88-91]

The inclusion criteria were: (1) patients aged 66 years or older at the time of mNSCLC diagnosis, (2) initiation of first-line ICI treatment within six months of mNSCLC diagnosis, and (3) continuous enrollment in Medicare Part A and Part B from six months prior to diagnosis through the initiation of ICI treatment. ICIs and chemotherapy were identified from Medicare Part B claims using HCPCS codes. First-line ICI treatment was defined as the initial treatment administered following diagnosis. The exclusion criteria were: (1) Medicare beneficiaries who received ICIs, chemotherapy, or radiation within six months prior to their metastatic cancer diagnosis, (2) those who received chemotherapy or radiation after diagnosis and before ICI initiation, and (3) those who initiated first-line treatment more than six months after diagnosis.[92]

3.2.2.4. Treatment Strategies and Assignment

In the hypothetical target trial, eligible individuals were randomly assigned to receive ICI-Chemotherapy or ICI-Monotherapy. Chemotherapy utilization for each cycle was identified using a 3-week (21-day) interval, consistent with clinical trial protocols.[101-103] In the second target trial, patients who initiated first-line ICI-Chemotherapy and completed at least 4 cycles of chemotherapy were assigned to either continue chemotherapy (6 cycles) or stop after 4 cycles. Observational analyses were designed to emulate randomized treatment assignments and treatment adherence by adjusting for potential baseline and time-varying confounders. At baseline, we accounted for demographic characteristics (age, sex, race, metropolitan status, geographic region, year of cancer diagnosis, and the Yost Index of socioeconomic status) as well

as clinical factors (tumor histology, concurrent radiation during first-line treatment, adjusted CCI excluding cancer, and the time from cancer diagnosis to the initiation of treatment).[104] Patient characteristics and NSCLC histology were assessed at the time of diagnosis. adjusted CCI was calculated using Medicare claims data from the six months before the ICI initiation.[105, 106] To account for evolving prognostic factors and changes in treatment patterns, we incorporated time-varying covariates updated every 21 days (3 weeks), including ICI adherence, emergency department visits, updated CCI, and adverse events including pneumonitis, diarrhea, hypothyroidism, and acute kidney injury (AKI).[105, 106] Emergency department visits and AEs were identified using HCPCS and ICD-9/10 codes.

3.2.2.5. Outcomes, Time Zero, and Follow-up

The primary outcome was OS (all-cause mortality). We used the Medicare date of death, which is validated against the National Death Index.[107] Follow-up began on the date of first-line ICI initiation (time zero) and ended at the earliest occurrence of one of the following events: (1) death; (2) loss of Medicare Part A or B enrollment; (3) the administrative cutoff date of December 31, 2020; or (4) completion of a 72-week follow-up period. In the second target trial, only patients who initiated first-line ICI-Chemotherapy and adhered to four cycles of chemotherapy were included. For this trial, time zero was defined as the initiation of the fifth cycle of ICI-Chemotherapy. The maximum follow-up duration was limited to 60 weeks since the first 12 weeks (four cycles) were incorporated into the inclusion criteria.

3.2.2.6. Causal Contrast

Our causal contrast of interest was the modified ITT and PP effects. In the first target trial, the modified intention-to-treat effect is the effect of ICI-Chemotherapy initiation vs ICI-Monotherapy initiation (the intention-to-treat effect would be the effect of assignment to one of

these strategies).[108] For the PP effect in the first trial, patients assigned to ICI-Chemotherapy who discontinued chemotherapy within 4 cycles, and those assigned to ICI-Monotherapy who subsequently received ICI-Chemotherapy, were censored at the time of deviation. In the second trial, patients assigned to a 4-cycle regimen who received additional chemotherapy within the next two cycles were censored at such cycle, and those assigned to 6 cycles who did not receive chemotherapy at the fifth or sixth cycle were censored at that time.

3.2.2.7. Statistical Analysis

Patient characteristics were summarized descriptively, and chemotherapy utilization was visualized by plotting the proportion of patients receiving chemotherapy at each treatment cycle. We employed a clone-censor-weight approach to address potential immortal time bias, where patients receiving chemotherapy might inherently survive longer.[109] Initially, all patients who initiated first-line ICIs were duplicated (cloned) and assigned to both ICI-Chemotherapy and ICI-Monotherapy groups. Under the modified ITT analysis, patients assigned to ICI-Monotherapy who received chemotherapy in cycle 1 and those assigned to ICI-Chemotherapy who did not receive chemotherapy in cycle 1 were censored at that point. For the PP analysis, patients in the ICI-Chemotherapy group who discontinued chemotherapy within the first 4 cycles and those in the ICI-Monotherapy group who initiated ICI-Chemotherapy during the whole follow-up were censored at the time of deviation.[101-103]

We applied stabilized inverse probability of censoring weights (sIPCW) to construct a pseudopopulation in which time-varying prognostic factors were independent of deviations from the assigned treatment.[110] To derive sIPCW, we first fitted a numerator model using pooled logistic regression that included the assigned treatment groups, time (modeled as cycles using four-knot restricted cubic splines), interaction terms between assigned treatment groups and time,

and all baseline covariates. The denominator model had the same core specifications but additionally incorporated one-cycle lagged values of the time-varying covariates.

$$sIPCW_t = \prod_{k=0}^{t} \frac{f(C_t = 0 |\, V_0, C_{t-1} = 0)}{f(C_t = 0 | V_0, L_{t-1}, C_{t-1} = 0)}$$

Here, $C_t = 0$ indicated the individual remained uncensored at time *t*. V_0 represented baseline covariates, and L_{t-1}represented the one-cycle lagged time-varying covariates updated in each cycle. Stabilized weights were calculated as the cumulative product of the predicted probabilities from the numerator model divided by those from the denominator model.

Next, we applied a weighted discrete-time hazards model via pooled logistic regression to model the probability of death.

$$Logit(\, h(t \mid X)) = \beta_0 + \beta_1\, (treatment) + \beta_2\, \left(S_j(t)\right) + \beta_3\, \left(treatment\, \times S_j(t)\right) +\, \sum_{j=4}^{j} \beta_j\, \times X_j$$

In this model, $h(t \mid X)$ represented the hazard at time t, conditional on the treatment strategy and baseline covariates. β_1 indicated the main treatment effects. $\beta_2\, \left(S_j(t)\right)$ modeled the effect of time on the hazard using 4-knot restricted cubic splines. The interaction term β_3 accounted for the time-dependent change in treatment effect at time t. $\sum_{j=4}^{j} \beta_j$ adjusted for the effects of all the baseline covariates.

We standardized the model-based estimates to the joint distribution of baseline characteristics to obtain adjusted, treatment-specific risks per cycle. Specifically, using the fitted model coefficients and the 'cloned' population with identical baseline covariate distributions across both groups, we calculated survival probabilities for each cycle and generated the survival

curves. Additionally, we estimated 72-week survival probabilities, 72-week RMST, and the HR using RMST and CPH models in the cloned population. The 95% CIs of 72-week survival difference, RMST difference, and HR were generated from 300 resample nonparametric bootstraps.

In the second target trial, we examined the PP effect of receiving 4 vs 6 chemotherapy cycles among patients already on ICI-Chemotherapy. Patients who initiated first-line ICI-Chemotherapy and completed 4 cycles of chemotherapy were identified, then "cloned" and assigned to either a 4-cycle or a 6-cycle chemotherapy strategy. In the 4-cycle group, individuals continuing chemotherapy beyond 4 cycles were censored at that point, while in the 6-cycle group, those discontinuing chemotherapy prior to 6 cycles were censored. After applying sIPCW to mitigate selection bias, we estimated survival probabilities, RMST differences, and HRs standardized to baseline characteristics, as described above.

One limitation of our analysis was the definition of a treatment cycle. Although clinical trials often define chemotherapy cycles as 21 days, real-world practice may involve longer intervals. Following a literature review and consultation with clinicians, we adopted a 28-day (4 weeks) cycle length to reflect real-world chemotherapy administration patterns and accommodate time-varying covariates in a sensitivity analysis.[101-103, 111] In this sensitivity assessment, we extended the maximum follow-up time to 96 weeks for ICI-Chemotherapy vs. ICI-Monotherapy and 80 weeks for 4 vs 6 cycles of chemotherapy in the second target trial, corresponding to 24 cycles of 4 weeks each.

3.3. Aim 2: To develop machine learning models for the prediction of irAEs after ICI initiation among patients with mNSCLC

3.3.1. Research question

Which factors can predict the risk of irAEs in patients with mNSCLC following first-line ICI treatments?

3.3.2. Data sources

We developed predictive models and tested the performance using the 2014-2020 SEER-Medicare data.[85]

3.3.3. Study sample

Patients were eligible if they were aged 66 years or older, diagnosed with mNSCLC between January 1, 2015, and December 31, 2019, and received first-line ICI therapy (pembrolizumab, nivolumab, or atezolizumab) within six months after diagnosis. Given that one cycle of first-line treatment typically spans 21 days, first-line ICI treatment was defined as the initiation of ICIs within 21 days following the start of anticancer therapy.[34, 63] MNSCLC was identified using the ICD-O-3 codes within the SEER database **(**Table 8**)**. ICI treatments were confirmed through Medicare claims based on the HCPCS codes (Table 9). To capture complete clinical and claims data, patients were required to have continuous enrollment in Medicare Parts A and B for at least six months before cancer diagnosis through the initiation of ICI therapy. Patients enrolled in Medicare Advantage plans within six months prior to cancer diagnosis or those with missing data were excluded from the study.

3.3.4. Feature selection

We included seven broad classes of features that are relevant and available in the SEER-Medicare database to predict irAEs after ICI initiation: (1) demographic variables: age, residence, sex, and race/ethnicity, (2) socioeconomic status: household median income, percentage of household with an education level below high school, and Yost scores, (3) baseline adjusted Charlson Comorbidity Index, (4) days from diagnosis to the initiation of ICI treatments, (5) other first-line cancer treatments: chemotherapy and radiation, (6) ICI treatment agents: pembrolizumab, nivolumab, and atezolizumab, (7) preexisting disease conditions.
Patients' demographics and socioeconomic status were obtained from SEER cancer registry data files. Comorbidities and preexisting conditions were identified using ICD-9 and ICD-10 diagnosis codes recorded in Medicare claims during the six months prior to cancer diagnosis. ICI treatment, chemotherapy, and radiation were captured using HCPCS and ICD-9/ICD-10 codes.[112, 113]

3.3.5. Outcome

As most irAEs occur around three months of ICI initiation, our primary outcome is the occurrence of irAEs within three months after initiating ICI treatments (Table 13). [29, 31, 114] Pneumonitis, as a pulmonary system irAE, was identified as the most frequent irAE for patients with NSCLC after ICI treatments.[31, 32] In addition, GI irAEs such as diarrhea, colitis, and hepatitis are also among the most frequent irAEs observed with ICI treatments.[30] GI irAEs tend to be more severe and potentially life-threatening compared to irAEs affecting other organ systems.[30] We predicted the risk of pneumonitis and GI irAEs within three months after ICI initiation as the second outcome.

Table 13. International classification of diseases codes for identifying irAEs

Organ system	Category	ICD-9 codes	ICD-10 codes
Dermatologic	Eruption	693.0	L27.0, L27.1
	Pruritus	698.8	L29.8, L29.9
	Lichen planus	697.0	L43.x, L44.3, L66.1
	Vitiligo	709.00, 709.01, 709.09	L80, L81.8, L81.9
	Bullous Pemphigoid	694.5	L12.0
	Stevens-Johnson syndrome/ toxic epidermal necrolysis	695.13, 695.14	L51.1, L51.3
Hematologic	Anemia	285.3, 285.8, 285.9284.x, 283.x	D59.x, D61.x, D60.x, D64.2, D64.3, D64.8
	Thrombocytopenia	287.3, 287.31, 287.8, 287.9, 287.31, 287.32, 287.4, 287.49, 287.5287.8, 287.9	D69.3, D69.41, D69.49, D69.59, D69.6
	Leukopenia	288.00, 288.03, 288.09 288.4, 288.5x, 288.8, 288.9	D72.1, D72.81, D72.810, D72.818, D72.819, D70.9, D70.4, D70.2, D76.1, D76.3
Pulmonary	Pneumonitis	508.8, 508.9, 486.x, 516.3x, 516.9	J84.11x, J70.9, J70.8, J70.2, J70.3, J70.4, J18.9, J84.89, J84.9
Liver	Hepatitis	573.3, 790.5	K71, R74.8, K75.4, K75.9, R94.5
Gastrointestinal	Diarrhea	787.91, 564.5	K59.1, K58.0, R19.7
	Colitis	558.2, 558.3, 558.4, 558.9, 555, 556.8, 556.9	K52.1, K52.29, K52.3, K52.9, K52.89, K53.82
	Pancreatitis	577.0	K85.x
	Mucositis	528.x	K12.30, K12.31
Endocrine AEs	Hypothyroidism	244.3, 244.8, 244.9	E03.2, E03.8, E03.9
	Hyperthyroidism	242	E05.x
	Hypophysitis	253.8	E23.6

	Adrenal insufficiency	255.41	E27.1, E27.3, E27.4
	Diabetes Type I	250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93	E09.x, E10.x, E13
	Cushing's syndrome	255.0	E24.9, E24.0, E24.2
	Hypopituitarism	253.2, 253.7	E23.0, E23.1, E23.3
	Thyroiditis (acute thyroiditis, subacute thyroiditis, iatrogenic thyroiditis, thyroiditis unspecified)	245.1, 245.4, 245.9	E06.0, E06.1, E06.9
Renal	Acute Kidney Injury	584.x	N17.x
	Acute interstitial nephritis	591.10, 591.11, 583.89	N10.x, N12.x, N14.1, N14.2
	Glomerulonephritis	580.x, 581.x, 583.x	N00.x, N01.x, N04.x, N05.x N06.x,
Cardiac	Arrhythmia	427.x	I48.x, I47.x, I49.x, I46.x
	Acute MI	410.x	I21.x
	Myocarditis	422.x, 429.x	I40.x, I51.4, I51.8, I51.9
	Pericarditis	420.x, 423.x	I30.x I31.4, I31.8-9
	Cardiomyopathy	425.4, 425.9	I42.0, I42.7, I42.9
Musculoskeletal	Dermatopolymyositis/ polymyositis	710.3, 710.4	M33
	Rheumatoid arthritis	714.x	M05, M06, M08.0, M08.2, M08.3, M08.4, M08.8, M08.9, M12.0
	Myalgia	729.1	M79.1
	Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA)	725, 446.5	M35.5, M31.5, M31.6
	Neuritis/neuralgia	729.2	M79.2
	Meningitis	047.9, 322.9	G03.9, A87.9

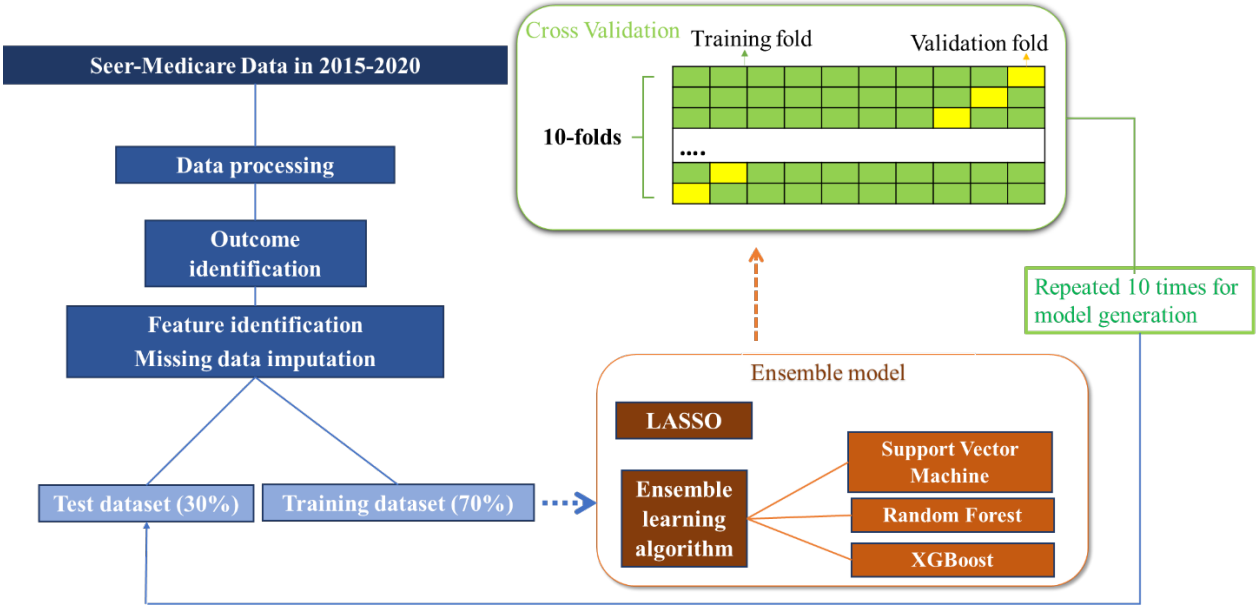
Central Nervous System (CNS)	Encephalitis/myelitis/ encephalomyelitis	323.8, 323.81, 323.82, 323.7, 323.71, 323.72, 323.9	G92, G04.81, G04.89, G04.90, G04.91
	Guillain-Barre syndrome	357.0	G61.0
	Myasthenia gravis	358.0	G70.0
	Peripheral neuropathy	357.89	G64

3.3.6. Algorithms, model training and validation

IrAEs are identified from inpatient and outpatient Medicare claims using ICD-9/ICD-10 and HCPCS codes (Table 13).[115] The SEER-Medicare dataset was randomly split at the patient level into training (80%) and test (20%) sets. The test set was used exclusively for evaluating model performance. We developed predictive models using LASSO logistic regression and three ML algorithms: RF, XGBoost, and SVM with a radial basis function kernel. Each model was trained using tenfold cross-validation to enhance predictive accuracy and reduce variability (Figure 2).

To reduce overfitting and improve reproducibility, we included only the most relevant features for predicting irAEs. LASSO logistic regression, which applies an L1 penalty, inherently performed both feature selection and regularization, thereby eliminating the need for additional selection steps.[116, 117] For RF, SVM, and XGBoost models, we used a recursive feature elimination algorithm. This approach began with all features and iteratively removed the least important ones based on feature importance rankings.[118, 119] The elimination process continued until the highest area under the receiver operating characteristic curve (AUROC) was achieved. The final feature set at this point was selected as the optimal input for each model.

Figure 2. Overview of predictive model development



3.3.7. Evaluation of prediction performance

We evaluated model performance using classification accuracy, F1 score, and AUROC. These metrics were calculated using the test dataset to ensure an unbiased assessment of each model's predictive capability. Among them, AUROC served as the primary metric for selecting the best-performing model for forecasting irAE risk.[120] AUROC evaluates a model's ability to distinguish between patients who will and will not experience irAEs across all classification thresholds.[120] It is robust to class potential imbalance sample size, making it a reliable metric for model performance evaluation.

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN}$$

$$F1\ score = \frac{2TP}{2TP + FP + FN}$$

TP: true positive TN: true negative FP: false positive FN: false negative

We adjusted the decision threshold to align with the true event probability, rather than relying on the default threshold of 0.50.[120] To reduce potential sampling bias and ensure robustness, we repeated the entire process of data splitting, training, and testing 100 times.[121] We reported the average model performance and corresponding 95% CI across these iterations.

3.3.8. Evaluation for feature importance

LASSO logistic regression automatically selected relevant features through the L1 penalty, enhancing both model performance and interpretability. In the three-based models (RF and XGBoost), feature importance was assessed by the mean decrease in the Gini index, which reflects how much each feature contributed to reducing node impurity. A higher mean decrease indicated greater importance.[122] For SVM, feature importance was evaluated based on each feature's effect on AUROC. The best-performing model among the four candidates was selected as the final model for assessing feature importance.

We calculated Shapley Additive exPlanations (SHAP) values to understand how the predictive model decides. SHAP is a method for interpreting machine learning models by quantifying the impact of each feature on the model's predictions. It utilizes the concept of Shapley values from cooperative game theory to allocate a fair contribution of each feature towards the prediction outcome, offering both local and global insights into model behavior.[123] To determine the effect of each feature on predicting irAEs after treatment, we compute the SHAP value for every feature for each patient. This calculation allows for an individualized (patient-specific) interpretation of the model's decision-making process. Additionally, by taking the average of the absolute SHAP values across all features, we gain insight into which features are generally most important to the model's predictions from a global (group-wide) perspective. Moreover, the SHAP value indicates the direction of a feature's influence on the model's

prediction: a positive SHAP value suggests that the feature increases the likelihood of predicting the presence of irAEs.

3.3.9. Potential challenges and alternative approaches

Firstly, we were unable to include certain important variables in our predictive models, such as BMI, PD-L1 expression levels, and gene mutation status, due to their absence in the SEER-Medicare dataset. As a result, the model performance may be suboptimal (AUROC<0.7). We would explore the feasibility of predicting specific subtypes of irAEs (e.g., endocrine-related irAEs) to achieve fair model performance.

3.4. Aim 3: To compare the cost-effectiveness of first-line cemiplimab plus chemotherapy with pembrolizumab plus chemotherapy for mNSCLC patients.

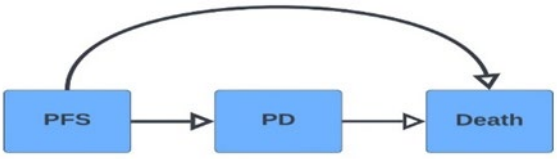
3.4.1. Research question

Is the first-line CCT cost-effective compared with PCT for mNSCLC patients?

3.4.2. Study design

From the U.S. Medicare and Medicaid payer perspective, we constructed a partitioned survival model to simulate costs, quality of life, toxic effects, disease progression, and survival for patients with mNSCLC treated with either first-line CCT or PCT (Figure 3).[124]

Figure 3. Partitioned survival model



PD: progressed disease; PFS: progression-free survival.

3.4.3. Survival model

The OS and PFS probabilities for patients treated with first-line CCT and PCT were derived from the EMPOWER-Lung 3, KEYNOTE-407, and KEYNOTE-189 trials. [23, 38, 41] KM survival curves were extracted using WebPlotDigitizer to capture the time-dependent probabilities of patients in progression-free states and PD states.[125] Subsequently, individual patient data (IPD) were simulated based on KM curves and fitted into standard parametric models, including exponential, Weibull, log-logistic, and log-normal distributions. The values of the Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used as metrics for the goodness of fit across the different parametric distributions. The models with the lowest AIC and BIC values were selected as the final survival distributions.

Patients with different histological subtypes of mNSCLC exhibited varying levels of treatment efficacy with PCT and CCT.[23, 38, 41] In the EMPOWER-Lung 3 trial for CCT, 42.9% of patients with aNSCLC exhibited squamous histology, while 57.1% had non-squamous histology.[41] To maintain consistency in the patient histology profile, the final OS and PFS models for PCT combined survival probabilities of squamous patients from KEYNOTE-407 and nonsquamous patients from KEYNOTE-189, with proportions of 42.9% and 57.1%, respectively.

3.4.4. Cost and utilities

This study included direct medical costs of therapeutic drugs, intravenous injection, administration, follow-up care, and severe adverse events (SAEs) management. [40-44]

Unit drug costs were derived from the Centers for CMS April 2024 Average Sales Price (ASP) drug pricing files.[39] Since the types of chemotherapy regimens differed among the KEYNOTE-407, KEYNOTE-189, and EMPOWER-Lung 3 trials, the costs of chemotherapy were calculated individually for each trial instead of using a uniform cost. The costs of administration for intravenous injection were derived from the CMS Physician Fee Schedule.[126] EMPOWER-Lung 3 did not report second-line treatment after CCT. KEYNOTE-407 and KEYNOTE-189 reported varied second-line treatment strategies based on clinicians' choices. Based on the literature review and expert opinions, we adopted the cost of best-supportive care after mNSCLC progression as the cost of second-line treatment for both groups.[44, 127, 128] We captured the treatment costs of SAEs, defined as grade ≥ 3 AEs with more than 5% incidence in the clinical trials. The cost of best-supportive care and management costs associated with SAEs were derived from the literature.[127, 129, 130] The weighted average cost of treating SAEs was calculated and input into the PSM model.[130] All costs were adjusted to 2024 U.S. dollars using the U.S. Consumer Price Index.[131, 132]

The effectiveness of treatment was measured using QALYs. Health utility was measured on a scale from 0 to 1, where 1 represents optimal health, and 0 represents death. The baseline values for health utilities in the progression-free states and PD states were sourced from the published literature.[131, 133] SAEs resulted in a decrement in their health utility, also known as disutility. Same as OS and PFS, the weighted averages of cost and disutility for PCT with

squamous and non-squamous lung cancer were calculated from KEYNOTE-407 and KEYNOTE-189, using proportions of 42.9% and 57.1%, respectively.[131, 133] For dosing calculations, we assumed that the patient weighs 70 kg, has a body surface area of 1.86 m^2, and a creatinine clearance of 70 mL/min, according to previous cost-effectiveness analyses of immunotherapies for patients with mNSCLC. [80, 134]

3.4.5. Base-case, sensitivity, and subgroup analyses

In the base-case analysis, we calculated the total costs and QALYs gained for patients with mNSCLC treated with first-line CCT and PCT. The incremental cost and incremental QALYs between CCT and PCT were then used to calculate the ICER

$$ICER = \frac{COST_{cemiplimab\ plus\ chemotherapy} - COST_{pembrolizumab\ plus\ chemotherapy}}{QALY_{cemiplimab\ plus\ chemotherapy} - QALY_{pembrolizumab\ plus\ chemotherapy}}$$

There were two main concerns in the base-case analysis. First, the disutility of SAEs for PCT was higher due to longer follow-up times. According to up-to-date published results, patients under treatment of CCT were followed for three years in the EMPOWER-Lung 3 trial, while those with PCT were followed for five years in the KEYNOTE-407 and KEYNOTE-189 trials. Secondly, the survival probability in the primary analysis was solely based on clinical trials. We, therefore, performed two scenario analyses. In scenario analysis 1, the incidence of SAEs for PCT was derived from the same follow-up time as CCT in the midterm reports of the KEYNOTE-407 and KEYNOTE-189 trials. Scenario analysis 2 extrapolated the OS curve after 60 months using mNSCLC relative survival rates from the 2000-2020 U.S. SEER data.[135] The survival rate from SEER was fitted to a Weibull distribution.

We also conducted a one-way deterministic sensitivity analysis (DSA) of costs, health utilities, and SAEs-related disutility to identify variables that significantly impacted the uncertainty of the ICER. To further assess model uncertainty, we performed a probabilistic sensitivity analysis (PSA) using a Monte Carlo simulation with 10,000 iterations. Cost-related variables were modeled using gamma distributions, while utility-related variables were modeled using beta distributions in the PSA.

Patients with mNSCLC exhibited different treatment efficacy with PCT and CCT across different PD-L1 expression levels. [23, 38, 41] For the subgroup analyses, we compared the cost-effectiveness of CCT versus PCT as the first-line treatment for patients with mNSCLC at different PD-L1 levels: ≥50%, 1%-49%, and <1%. The EMPOWER-Lung 3, KEYNOTE-407, and KEYNOTE-189 trials reported the HRs of OS and PFS for CCT and PCT compared to chemotherapy alone at different PD-L1 levels.[23, 38, 41] To derive the HR between CCT and PCT at different PD-L1 levels, we conducted a fixed-effect network meta-analysis (NMA) using the "netmeta" package in R.[136] First, we extracted the HRs for OS and PFS, along with their 95% CIs, for CCT and PCT compared to chemotherapy alone from the EMPOWER-Lung 3, KEYNOTE-407, and KEYNOTE-189 trials. [23, 38, 41] Next, we employed a fixed-effect model in the network meta-analysis to calculate the HRs between CCT and PCT at different PD-L1 levels. The OS and PFS for PCT were calculated by raising the OS and PFS of CCT to the power of the HRs between PCT and CCT.

$$OS_{PCT} = {OS_{CCT}}^{HR_{OS}}$$

$$PFS_{PCT} = {PFS_{CCT}}^{HR_{PFS}}$$

3.4.6. Potential challenges and alternative approaches

In the PSM, PFS and OS were assumed to be independent and extrapolated independently beyond the trial follow-up to ten years. Failure to account for dependencies between PFS and OS may affect the accuracy of extrapolated efficacy and undermine the validity of the results. Moreover, no clinical trial has directly compared CCT and PCT. The EMPOWER-Lung 3 trial evaluating CCT included 14.8% of patients with unresectable locally advanced NSCLC and 85.2% with mNSCLC. Therefore, conclusions regarding the comparative effectiveness and safety of CCT versus PCT for mNSCLC should be interpreted with caution.

Chapter 4: Results

Aim 1.1 Manuscript

Title: Comparative Real-World Survival of First-Line Atezolizumab, Nivolumab, and Pembrolizumab in Older Patients with Metastatic Non–Small Cell Lung Cancer

Abstract:

Objective: While immune checkpoint inhibitors (ICIs) have significantly improved overall survival (OS) for patients with metastatic non–small cell lung cancer (mNSCLC), there is a paucity of comparative effectiveness evidence to inform optimal first-line treatment selection. This study compared OS among older patients with mNSCLC who received first-line atezolizumab, nivolumab, or pembrolizumab.

Methods: This retrospective cohort study used the 2014-2020 SEER-Medicare data and included patients aged 66 years or older, diagnosed with mNSCLC, and treated with first-line atezolizumab, nivolumab, or pembrolizumab. OS was compared using unadjusted, multivariable-adjusted, and propensity score matching (PSM) Cox proportional hazards models. Sensitivity analyses among treatment-adherent patients and subgroup analyses stratified by tumor histology were also conducted.

Results: The study cohort included 4,635 patients, 112 treated with atezolizumab, 251 with nivolumab, and 4,272 with pembrolizumab. Pembrolizumab was associated with a significant survival advantage compared to atezolizumab (multivariable-adjusted hazard ratio (HR)=0.67; 95% confidence interval (CI)=0.53-0.84; PSM HR=0.69; 95% CI=0.54-0.87) and nivolumab (multivariable-adjusted HR=0.83; 95% CI=0.69-0.99). The OS difference between nivolumab and atezolizumab was inconclusive (multivariable-adjusted HR=0.73; 95% CI=0.46-1.16; PSM

HR=0.65; 95% CI: 0.41-1.04). These findings were consistent across sensitivity analyses. In subgroup analyses, differences in OS between pembrolizumab and nivolumab were inconclusive among patients with squamous histology (multivariable-adjusted HR=0.85; 95% CI=0.65-1.11; PSM HR=1.15; 95% CI=0.89-1.49).

Conclusion:

In this population-based study, first-line pembrolizumab was associated with a significant OS benefit compared with atezolizumab and nivolumab among older adults with mNSCLC. For patients with squamous histology, OS differences between pembrolizumab and nivolumab were inconclusive. These findings support pembrolizumab as the preferred first-line treatment for older patients with mNSCLC, while highlighting the need for further investigation into the comparative effectiveness of nivolumab in squamous histology subgroups.

Introduction

Lung cancer is the second most prevalent cancer and the primary cause of cancer-related death in both men and women in the United States (U.S.).[1] In 2023, there were 238,340 new cases of lung cancer and 127,070 fatalities in the U.S., accounting for 12.2% of total cancer incidence and 20.8% of cancer deaths.[1, 2] Non-small cell lung cancer (NSCLC) accounts for 80-85% of all lung cancer cases.[3] Around 70% of patients with lung cancer are in advanced or metastatic stages at diagnosis, and the five-year relative survival is only 9% for metastatic NSCLC (mNSCLC). [137]

Immunotherapy has significantly improved the survival outcomes of mNSCLC patients. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that block specific proteins in immune cells and cancer cells, enhancing the immune system to recognize and attack cancer cells. In March 2015, nivolumab was approved by the U.S. Food and Drug Administration (FDA) as the first ICI to treat mNSCLC.[8] Since then, seven ICIs (nivolumab, pembrolizumab, cemiplimab, atezolizumab, durvalumab, ipilimumab, and tremelimumab) have been approved and launched as the first-line treatments for mNSCLC in the U.S.[7]

The FDA's approvals of ICI treatments were based on several phase III clinical trials, which demonstrated superior efficacy compared to chemotherapy alone.[17-26, 45] However, the comparative efficacy of various ICIs remains unclear due to the lack of direct, head-to-head clinical trials. Real-world evidence can provide valuable insights into treatment effectiveness when clinical trials are unavailable. Two previous studies compared the effectiveness of different ICIs but failed to identify significant differences in overall survival (OS), possibly because of small sample sizes, with merely 49 and 146 patients treated with pembrolizumab in each study, respectively. [138, 139] Given the widespread adoption of ICIs for mNSCLC, it is critical to generate robust evidence to guide treatment decisions. This study aimed to systematically evaluate the

comparative OS of first-line atezolizumab, pembrolizumab, and nivolumab in patients with mNSCLC in the U.S.

Methods

Study design

This was a retrospective new user cohort study to compare the OS between three marketed ICIs (pembrolizumab, atezolizumab, and nivolumab) using the 2014-2020 Surveillance, Epidemiology, and End Results (SEER)-Medicare data.[85]

Data sources

The SEER-Medicare data represents the linkage of two expansive population-based data sources. It provides detailed insights into patients with cancer who are Medicare beneficiaries.[85] The SEER serves as the most extensive data repository for cancer research, covering 48% of U.S. cancer patients.[86] It collects and publishes data on patient demographics, primary tumor site, tumor characteristics, the initial treatment cause, and subsequent follow-ups. Medicare covers adults aged 65 and older, as well as patients under 65 who received social security disability insurance or diagnosed with end-stage renal disease in the U.S.[140] Medicare data includes inpatient and hospital care (Part A), physician services, outpatient care, skilled nursing facilities, home health services (Part B), and prescription drugs (Part D). The linkage of these two data sources creates a useful population-based database that can be used for an array of epidemiological studies (i.e., treatment patterns).[87] Given that nivolumab was approved as the first ICI treatment and marketed in the U.S. on March 4, 2015, this study utilized data from the

SEER cancer registry data spanning January 1, 2015, to December 31, 2019, and linked Medicare enrollment and claims data from January 1, 2014, to December 31, 2020.

Study Sample

This study included patients diagnosed with mNSCLC between January 1, 2015, and December 31, 2019, treated with first-line ICIs. The International Classification of Diseases for Oncology, third edition (ICD-O-3) codes from the SEER database (**Supplementary Table 1**) were used to identify patients with mNSCLC.[88-91]

The inclusion criteria were (1) aged 66 years or older at the time of mNSCLC diagnosis, (2) initiated first-line pembrolizumab, nivolumab, or atezolizumab in six months after mNSCLC diagnosis, and (3) continuously enrolled in Medicare Part A and Part B during six months before diagnosis and between diagnosis and the initiation of ICI treatments. Pembrolizumab, nivolumab, or atezolizumab and other ICI treatments were identified from Medicare Part B claims using Healthcare Common Procedural Coding System codes (HCPCS). First-line treatments were defined as the initial therapies after diagnosis. Given that one cycle of first-line treatment typically spans 21 days, patients who initiated chemotherapy or radiation after diagnosis but received immunotherapy within a 21-day window following chemotherapy or radiation were also classified as receiving first-line ICI treatments.[34, 63] The exclusion criteria were beneficiaries who (1) received ICIs, chemotherapy, and radiation six months before cancer diagnosis, and (2) initiated ICI treatment after six months of diagnosis. Chemotherapy and radiation were identified using HCPCS and ICD-9/10 codes (**Supplementary Table 1**).[92] The sample selection process was demonstrated in **Figure 1**. This study was approved by the institutional review board (IRB) for human subjects research at Auburn University.

Outcomes

The primary outcome was OS, measured in days from the initiation of first-line ICI treatment to death. Patients who disenrolled from Medicare Part A or Part B or reached the end of data availability were treated as censored at that time. The SEER-Medicare database provides date of death information from both SEER records and Medicare claims. We opted to use the Medicare date of death, as it is more up-to-date and validated by the National Death Index.[106, 141]

Covariates

The covariates included (1) patients' demographic characteristics (age, sex, race, metropolitan status, geographic region, and socioeconomic status as identified by the Yost index in SEER data, which reflects an individual's economic, social, and educational standing), (2) histology of mNSCLC (squamous and nonsquamous), (3) other first-line cancer treatments (chemotherapy, radiation), (4) modified Charlson comorbidity index, (5) autoimmune disease history, and (6) time from cancer diagnosis to treatment initiation (in days). Patients' characteristics and cancer histology were identified at the time of diagnosis. Autoimmune disease history was defined as the presence of systemic immune-mediated disorders involving multiple organ systems (**Supplementary Table 2**).[93] The modified CCI (excluding cancer) and autoimmune disease history were measured using Medicare claims data within 6 months before cancer diagnosis. [94] The identification of the new user cohort and baseline covariates was illustrated in **Supplementary Figure 1**.

Statistical analysis

The survival curves were generated using the Kaplan-Meier method, and treatment groups were compared using log-rank tests. Unadjusted univariable, multivariable-adjusted, and propensity score matching (PSM) Cox proportional hazards (CPH) models were utilized for the primary analysis. The proportional hazards (PH) assumption for each model was assessed using the Schoenfeld residual test, along with visual inspection of residual plots and Kaplan-Meier curves.[96] In the multivariable models, the PH assumption was evaluated for each covariate. For categorical variables that violated this assumption, we employed a stratified Cox proportional hazards model. Each stratum was assigned its own baseline hazard function, enabling variation in hazard rates across strata while maintaining the consistency of covariate effects across all strata. For continuous variables that violated the assumption, we incorporated time-varying coefficients to account for their non-proportional effects over time.[97] PSM models were employed as alternative estimators to check the robustness of the findings from the multivariable models. Instead of including all patients and all covariates in the outcome regression, the PSM approach generated two treatment groups in which the characteristics of patients were comparable. Propensity scores (PS) for receiving each pair of ICI treatments (e.g., pembrolizumab vs. atezolizumab) were estimated by multivariable logistic regression models. Patients were matched based on the nearest neighbor of estimated PS, with matching ratios of 1:5 for atezolizumab/nivolumab vs. pembrolizumab, and 1:1 for atezolizumab vs. nivolumab. Post-matching covariate balance was assessed using standardized mean differences (SMD). Covariates were well balanced between atezolizumab/nivolumab and pembrolizumab after matching. (SMD < 0.1). Cox proportional hazards models were fitted with treatment group as the primary exposure in the matched cohort. For the atezolizumab vs. nivolumab comparison, several covariates—such as age and geographic region—remained imbalanced after matching.

To address this, unbalanced covariates were included as additional covariates in the post-matching outcome model along with the treatment group indicator.[95]

To evaluate the treatment's effectiveness among adherent patients and minimize confounding from ICI treatment switching, we conducted a sensitivity analysis by applying two conditions: including patients who continuously used ICIs for at least three months after initiation and censoring patients upon switching to another ICI. We also conducted subgroup analyses to identify variations in treatment effectiveness for different histology patients and ICI regimens. Specifically, we performed subgroup analyses for patients with nonsquamous or squamous histology and those receiving ICI monotherapy or ICI plus chemotherapy as first-line treatment. For the comparisons between pembrolizumab and nivolumab in sensitivity analyses, and pembrolizumab-chemotherapy versus atezolizumab-chemotherapy in subgroup analyses, we found violations of the PH assumption, even after stratifying and adjusting for covariates. As a result, we used the Restricted Mean Survival Time (RMST) method for these two comparisons. RMST compared the average survival time over a specified period, without having to assume PH.[98] We applied univariable, multivariable, and PSM RMST models, calculating RMST ratios to comprehensively assess treatment effects. [99] Data cleaning was performed using SAS (version 9.4), and statistical analyses were conducted using “MatchIt,” “survival,” and “survRM2” in R (version 4.2.3)[142-144].

3. Results

Sample characteristics

After applying inclusion and exclusion criteria, we identified 4,635 mNSCLC patients treated with first-line ICIs. The cohort included 112 patients receiving atezolizumab, 251 receiving

nivolumab, and 4,272 receiving pembrolizumab, with median ages of 73, 79, and 75 years, respectively. Most patients were white (87.5%, 91.2%, and 90.4%) and resided in metropolitan areas (89.3%, 89.2%, and 85.3%) across the atezolizumab, nivolumab, and pembrolizumab groups, respectively. Atezolizumab had the highest concurrent chemotherapy use (84.8%), compared to only 7.2% for nivolumab. Nonsquamous histology was predominant across all treatment groups, with 93.8% in the atezolizumab group, 65.7% in the nivolumab group, and 80.1% in the pembrolizumab group. The prevalence of baseline autoimmune diseases ranged from 33.8% in the pembrolizumab group to 38.2% in the nivolumab group. The median time from cancer diagnosis to ICI initiation ranged from 50 days for atezolizumab and 61 days for nivolumab (**Table 1**). Patients treated with pembrolizumab had the longest median follow-up time at 306 days. The rate of treatment switching from initial ICIs to another ICI was 8.9% for atezolizumab, 9.2% for nivolumab, and 2.8% for pembrolizumab (**Table 2**). The characteristics of the matched cohorts are detailed in **Supplementary Tables 3-5**.

Results from the main analyses

The comparative effectiveness of OS demonstrated varying OS benefits among ICIs as first-line treatment for mNSCLC patients (**Table 2, Figure 2**). In the primary analysis, the OS was not significantly different between nivolumab and atezolizumab (unadjusted hazard ratio (HR)=0.90 with 95% confidence interval (CI): 0.70-1.16; multivariable-adjusted HR=0.73 with 95% CI: 0.46-1.16; and PSM HR=0.65 with 95% CI: 0.41-1.04). Pembrolizumab showed a significant survival benefit compared to atezolizumab, with HRs consistently indicating a lower hazard of death (unadjusted HR=0.69 with 95% CI: 0.56-0.86; multivariable adjusted HR=0.67 with 95% CI: 0.53-0.84; and PSM HR=0.69 with 95% CI: 0.54-0.87). In the comparison between pembrolizumab and nivolumab, pembrolizumab showed a survival benefit in unadjusted and

multivariable models (unadjusted HR=0.81 with 95% CI: 0.70-0.93; multivariable adjusted HR=0.83 with 95% CI: 0.69-0.99); however, statistical significance was not reached in the PSM model (PSM HR=0.87 with 95% CI: 0.75-1.02).

Results from the sensitivity analyses

When limited to patients who continuously used ICIs for at least three months and were censored at the time of ICI switching, the results were consistent with the main analyses (**Table 3, Supplementary Figure 2**). Nivolumab and atezolizumab had no conclusive difference in OS, and pembrolizumab demonstrated a significant survival benefit over atezolizumab. Pembrolizumab was associated with a significantly longer average survival time within a three-year follow-up compared to nivolumab (unadjusted RMST ratio=1.22 with 95% CI: 1.07-1.39; multivariable adjusted RMST ratio=1.24 with 95% CI: 1.08-1.43; PSM RMST ratio=1.17 with 95% CI: 1.01-1.34).

Results from subgroup analyses

In the subgroup analyses by histology, the results varied across ICIs (**Table 3, Supplementary Figures 3,4**). Among patients with nonsquamous histology, the OS between nivolumab and atezolizumab was not significantly different (unadjusted HR=0.96 with 95% CI: 0.72-1.27; multivariable adjusted HR=0.72 with 95% CI: 0.40-1.28; PSM HR=0.76 with 95% CI: 0.44-1.30). Pembrolizumab showed a significant survival benefit over atezolizumab (unadjusted HR=0.69 with 95% CI: 0.55-0.86; multivariable adjusted HR=0.69 with 95% CI: 0.54-0.87; PSM HR=0.74 with 95% CI: 0.58-0.94), also demonstrated a better survival outcomes compared to nivolumab (unadjusted HR=0.74 with 95% CI: 0.63-0.88; multivariable adjusted HR=0.74 with 95% CI: 0.62-0.88; PSM HR=0.82 with 95% CI: 0.68-0.99). Among patients with

squamous histology, no significant difference in OS was observed between pembrolizumab and nivolumab (unadjusted HR=0.94 with 95% CI: 0.73-1.21; multivariable adjusted HR=0.85 with 95% CI: 0.65-1.11; PSM HR=1.15 with 95% CI: 0.89-1.49).

In the subgroup analyses by treatment regimens, pembrolizumab-chemotherapy was associated with a significantly longer two-year survival compared to atezolizumab-chemotherapy (unadjusted RMST ratio=1.27, with 95% CI: 1.09-1.50; multivariable adjusted RMST ratio=1.27 with 95% CI: 1.08-1.49; PSM RMST ratio=1.26 with 95% CI: 1.05-1.50). Pembrolizumab monotherapy had no conclusive difference in OS as nivolumab monotherapy in the multivariable and PSM CPH model (unadjusted HR=0.85 with 95% CI: 0.73-0.99; multivariable adjusted HR=0.88 with 95% CI: 0.75-1.02; PSM HR=0.89 with 95% CI: 0.76-1.04).

Discussion

In this retrospective cohort study of older patients with mNSCLC, we assessed the real-world effectiveness in OS of three marketed first-line ICIs—pembrolizumab, nivolumab, and atezolizumab. We found that pembrolizumab was associated with significantly improved OS compared with atezolizumab (overall, among patients treated for at least three months, among patients with squamous histology, and between patients treated with pembrolizumab-chemotherapy vs. atezolizumab-chemotherapy). Pembrolizumab also demonstrated better survival outcomes compared with nivolumab in the unadjusted, multivariable, sensitivity analyses, and among patients with nonsquamous histology, though the difference was not statistically significant in the PSM model of main analyses, multivariable adjusted, and PSM models between patients treated with pembrolizumab and nivolumab monotherapies. Among patients with squamous histology, no significant difference in OS was observed between

pembrolizumab and nivolumab. Finally, nivolumab and atezolizumab had no significant difference in OS in all analyses.

Our findings contribute to the growing body of real-world evidence in ICIs. One retrospective cohort study of Korean veterans with mNSCLC reported higher objective response rates (ORR) and disease control rates (DCR) for pembrolizumab compared to atezolizumab and nivolumab. Specifically, the ORRs for pembrolizumab, nivolumab, and atezolizumab were 22.4%, 8.2%, and 4.3%, respectively ($p = 0.004$), while the DCRs were 59.2%, 55.7%, and 30.0%, respectively ($p = 0.001$). However, the study did not find statistically significant differences in OS between the three ICIs, with median survival times of 12.6 months, 8.4 months, and 7.7 months, respectively ($p = 0.334$). Given the relatively small sample size, particularly for pembrolizumab (N=49), the lack of statistical significance in OS may be attributed to limited statistical power. Our study builds on this evidence, demonstrating that first-line pembrolizumab was associated with significantly improved OS compared with both atezolizumab and nivolumab in a larger-scale, real-world new user cohort of older patients with mNSCLC. These findings not only reinforce the superior effectiveness of pembrolizumab in OS observed in previous studies but also are innovative for older patients, a population not specifically addressed in earlier research.

Additionally, the survival benefit of pembrolizumab over nivolumab appeared to vary by lung cancer histology. In patients with nonsquamous histology, pembrolizumab showed a clear OS advantage over nivolumab, whereas no significant difference was observed between the two ICIs in patients with squamous histology. To our knowledge, the effectiveness of first-line pembrolizumab and nivolumab has not been directly compared based on patients' histological subtypes. In addition, the CheckMate 227 Part 2 trial showed similar OS between nivolumab-

chemotherapy and chemotherapy alone as first-line treatment in patients with nonsquamous mNSCLC (HR = 0.86, 95% CI: 0.69–1.08). However, in patients with squamous mNSCLC, the analysis showed a significant OS benefit with nivolumab-chemotherapy than chemotherapy alone (HR = 0.69, 95% CI: 0.50–0.97).[103] Based on clinical trial results, nivolumab is not recommended as the first-line treatment for patients with mNSCLC in the updated National Comprehensive Cancer Network guideline.[145] Nevertheless, the combination of nivolumab plus ipilimumab is both an FDA-approved and NCCN-recommended first-line regimen for patients with mNSCLC.[145] Our findings may further inform ongoing evaluations of nivolumab plus ipilimumab or other dual nivolumab-based therapies by highlighting differences in efficacy and effectiveness across patients' histological subtypes.

This study has several limitations. First, we employed a "modified intention-to-treat" approach in the main analysis, in which patients were analyzed based on the treatment they initially received, regardless of subsequent change of therapy. This approach may have introduced bias by including patients who switched treatments or discontinued therapy early. To mitigate this potential bias, we conducted a sensitivity analysis requiring patients to remain on ICIs for at least three months after initiation and censoring those who switched treatments. This additional analysis confirmed the robustness of our primary findings. Secondly, the SEER-Medicare data lacks key clinical information, such as PD-L1 expression levels, smoking history, and genetic mutations (e.g., EGFR, ALK), which are critical for ICI treatment selection and prognosis. The absence of these variables resulted in residual confounding, potentially biasing the observed treatment effects. Additionally, patients enrolled in managed care were not excluded due to sample size considerations. Alongside managed care enrollment, factors such as coding inaccuracies and variability in clinical practice and administrative claims data may affect

treatment classification and outcome assessments, potentially introducing measurement bias.[146] Finally, our cohort was limited to Medicare beneficiaries, which may limit the generalizability of the findings to other populations.

Our findings hold substantial implications for the clinical management of mNSCLC. First, pembrolizumab demonstrated a significant OS benefit compared to atezolizumab and nivolumab, supporting its role as the superior first-line ICI for patients with mNSCLC. Moreover, the comparable OS between pembrolizumab and nivolumab in patients with squamous mNSCLC provides potential flexibility in selecting an appropriate ICI based on individual patient characteristics and preferences. In real-world clinical settings, findings from this study contribute to the advancement of standardized first-line treatment and evidence-based decision-making for mNSCLC, leading to improved patient survival outcomes and more efficient utilization of healthcare resources.

Figure 1. Flowchart of patient inclusion and exclusion

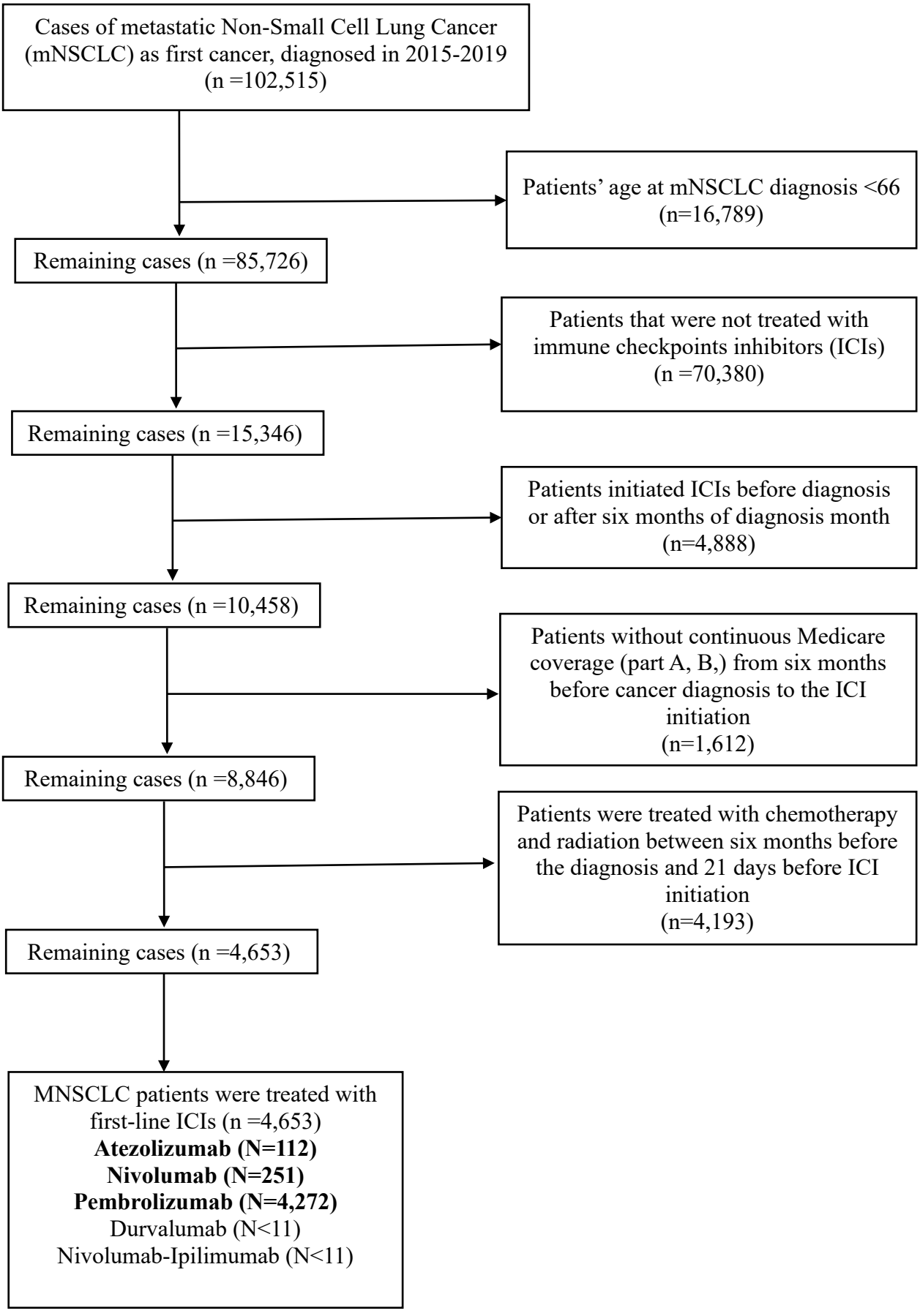


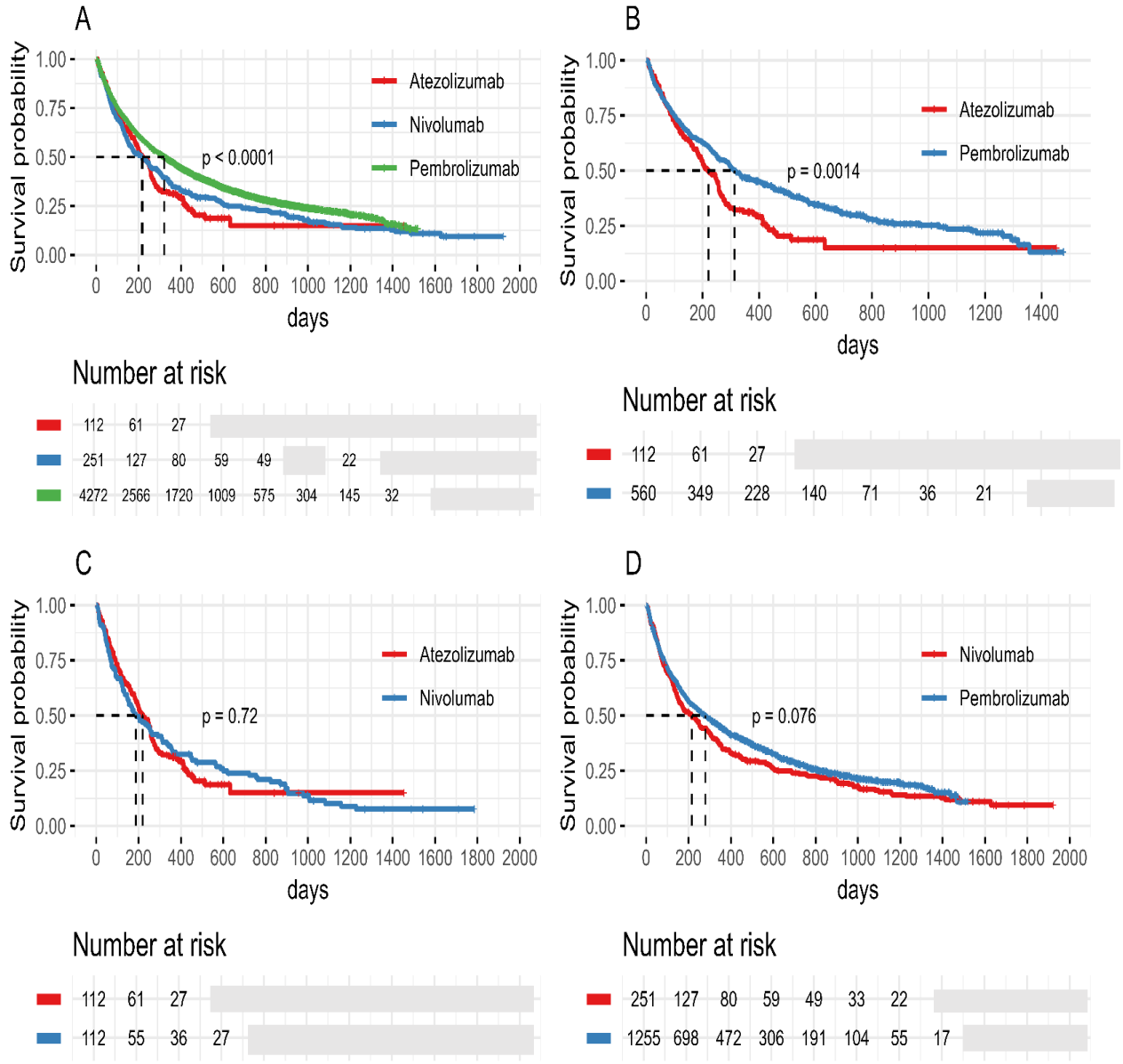
Figure 2. Survival probabilities of first-line pembrolizumab, nivolumab, and atezolizumab in patients with mNSCLC before and after propensity score matching

A. Survival probabilities of atezolizumab (N=112), nivolumab (N=251), and pembrolizumab (N=4272)

B. Survival probabilities of atezolizumab (N=112) and pembrolizumab (N=560) after propensity score matching

C. Survival probabilities of atezolizumab (N=112) and nivolumab (N=112) after propensity score matching

D. Survival probabilities of nivolumab (N=251) and pembrolizumab (N=1255) after propensity score matching



Suppressed due to a sample size of Ns < 11 or changes in the number of individuals at risk between time points of Ns < 11

Table 1. Patient Characteristics

Characteristic	Immune Checkpoint Inhibitor		
	Atezolizumab N = 112	**Nivolumab N = 251**	**Pembrolizumab N = 4,272**
Age (years) [1]	73.0 (69.0, 80.0)	79.0 (73.0, 84.0)	75.0 (71.0, 80.0)
Geographic Region			
Midwest	–	17 (6.8%)	325 (7.6%)
Northeast	>34 (>30.4%)*	77 (30.7%)	1,497 (35.0%)
South	31 (27.7%)	66 (26.3%)	1,252 (29.3%)
West	36 (32.1%)	91 (36.3%)	1,198 (28.0%)
Metropolitan Status			
Metropolitan	100 (89.3%)	224 (89.2%)	3,644 (85.3%)
Nonmetropolitan	12 (10.7%)	27 (10.8%)	628 (14.7%)
Sex			
Female	41 (36.6%)	119 (47.4%)	2,023 (47.4%)
Male	71 (63.4%)	132 (52.6%)	2,249 (52.6%)
Race			
Non-White	14 (12.5%)	22 (8.8%)	410 (9.6%)
White	98 (87.5%)	229 (91.2%)	3,862 (90.4%)
Yost index state quintiles (area level SES[2] deprivation)			
Group 1, lowest SES	–	22 (8.8%)	400 (9.4%)
Group 2, low-middle SES	20 (17.9%)	43 (17.1%)	753 (17.6%)
Group 3, middle SES	20 (17.9%)	57 (22.7%)	934 (21.9%)
Group 4, high-middle SES	28 (25.0%)	61 (24.3%)	1,014 (23.7%)
Group 5, highest SES	32 (28.6%)	57 (22.7%)	1,051 (24.6%)
Unknown, blank	–	11 (4.4%)	120 (2.8%)
Charlson Comorbidity Index			

>=2	41 (36.6%)	87 (34.7%)	1,185 (27.7%)
0	45 (40.2%)	101 (40.2%)	1,951 (45.7%)
1	26 (23.2%)	63 (25.1%)	1,136 (26.6%)
Tumor Histology			
nonsquamous	>101 (>90.2%)*	165 (65.7%)	3,422 (80.1%)
squamous	–	86 (34.3%)	850 (19.9%)
Autoimmune Disease History	40 (35.7%)	96 (38.2%)	1,442 (33.8%)
Chemotherapy	95 (84.8%)	18 (7.2%)	2,151 (50.4%)
Radiation Therapy	20 (17.9%)	33 (13.1%)	917 (21.5%)
Time to Treatment Initiation (days) [1]	49.5 (37.5, 67.0)	61.0 (43.0, 91.0)	56.0 (42.0, 74.0)

[1]Median with 25% lower bound and 75 % upper bound
[2]SES = socioeconomic status
–: suppressed due to cell size < 11
*: coarsened another category to suppress cells with size < 11 adequately

Table 2. Treatment duration, follow-up time, and hazard ratio of overall survival between atezolizumab, nivolumab, and pembrolizumab

	Atezolizumab	Nivolumab	Pembrolizumab
Number of patients	112	251	4272
Follow-up Time (days)*	220 (91, 394)	203 (74, 577)	306 (98, 577)
Treatment Switch	–	23 (9.2%)	119 (2.8%)
Hazard Ratio			
Unadjusted	Reference	0.90 (0.70, 1.16)	**0.69 (0.56, 0.86)**
Multivariable adjusted	Reference	0.73 (0.46, 1.16)	**0.67 (0.53, 0.84)**
Propensity score match	Reference	0.65 (0.40, 1.04)^	**0.69 (0.54, 0.87)#**
Unadjusted		Reference	**0.81 (0.70, 0.93)**
Multivariable adjusted		Reference	**0.83 (0.69, 0.99)**
Propensity score match		Reference	0.87 (0.75, 1.02)&

* Median with 25% lower bound and 75% upper bound
^ 112 patients treated with atezolizumab, and 112 patients treated with nivolumab after propensity score matching (PSM)
# 112 patients treated with atezolizumab, and 560 patients treated with pembrolizumab after PSM
& 251 patients treated with nivolumab, and 1255 patients treated with pembrolizumab after PSM
–: suppressed due to cell size < 11

Table 3. Subgroup and sensitivity analyses of the estimated treatment effect of different ICIs

	Unadjusted	Multivariable adjusted	Propensity score match
Sensitivity analysis			
Nivolumab vs Atezolizumab*	0.88 (0.63, 1.23)	0.67 (0.22, 2.03)	1.08 (0.48, 2.44)
Pembrolizumab vs Atezolizumab*	**0.58 (0.44, 0.76)**	**0.58 (0.43, 0.79)**	**0.65 (0.48, 0.87)**
Pembrolizumab vs Nivolumab^	**1.22 (1.07, 1.39)**	**1.24 (1.08, 1.43)**	**1.17 (1.01, 1.34)**
Subgroup analysis 1# Histology			
Nonsquamous			
Nivolumab vs Atezolizumab*	0.96 (0.72, 1.27)	0.72 (0.40, 1.28)	0.76 (0.44, 1.30)
Pembrolizumab vs Atezolizumab*	**0.69 (0.55, 0.86)**	**0.69 (0.54, 0.87)**	**0.74 (0.58, 0.94)**
Pembrolizumab vs Nivolumab*	**0.74 (0.63, 0.88)**	**0.74 (0.62, 0.88)**	**0.82 (0.68, 0.99)**
Squamous			
Pembrolizumab vs Nivolumab*	0.94 (0.73, 1.21)	0.85 (0.65, 1.11)	1.15 (0.89, 1.49)
Subgroup analysis 2# Treatment regimen			
Pembrolizumab-chemotherapy vs Atezolizumab-chemotherapy#	**1.27 (1.09,1.50)**	**1.27 (1.08,1.49)**	**1.26 (1.05,1.50)**
Pembrolizumab-monotherapy vs Nivolumab-monotherapy*	**0.85 (0.73,0.99)**	0.88 (0.75,1.02)	0.89 (0.76,1.04)

***** Hazard ratio
^ Three-year restricted mean survival time ratio
# Two-year restricted mean survival time ratio

Aim 1.2 Manuscript

Title: Comparative Survival of First-Line Immunotherapy plus Chemotherapy versus Immunotherapy Monotherapy in Older Adults with Metastatic Non-Small Cell Lung Cancer: An Emulated Target Trial Approach

Abstract

Purpose: The optimal use of first-line immune checkpoint inhibitors (ICIs) in combination with chemotherapy (ICI-Chemotherapy) for metastatic non–small cell lung cancer (mNSCLC) remains unclear. Our study aimed (1) to compare overall survival (OS) between ICI-Chemotherapy and ICI monotherapy (ICI-Monotherapy) as the first-line treatment for mNSCLC, and (2) to assess whether extending chemotherapy from four to six cycles improves OS within first-line ICI-Chemotherapy regimens.

Methods: We emulated two hypothetical target trials using SEER-Medicare data (2014–2020), including patients aged ≥66 years diagnosed with mNSCLC who initiated first-line ICI therapy. A Clone-censor-weight approach and discrete-time hazard models were applied to estimate the per-protocol (PP) treatment effect. OS was evaluated via survival curves, 72-week OS probabilities, restricted mean survival times (RMST), and hazard ratios (HR).

Results: In the first trial, PP analyses showed that ICI-Chemotherapy were associated with significant survival benefit over ICI-Monotherapy, including 5.5% (95% CI: 4.2%-6.7%) higher 72-week OS rate, 6.27-week RMST gain (95% confidence interval (CI), 4.88-7.61), and HR of 0.76 (95% CI, 0.71-0.81). In the second target trial, receiving six vs four chemotherapy cycles yielded 5.1% (95% CI: -0.9%-11.0%) higher 72-week OS rate, modest 2.19-week RMST increase (95% CI, 0.54-4.92), and HR of 0.83 (95% CI: 0.65-0.95).

Conclusions: In older adults with mNSCLC, adding chemotherapy to first-line ICI therapy confers a significant survival benefit compared with ICI-Monotherapy. Extending chemotherapy from four cycles to six cycles may further improve OS. These findings highlight the clinical importance of chemotherapy as a component of first-line ICI regimens in this population.

Introduction

Lung cancer is the second most common cancer and the leading cause of cancer-related deaths in the United States (U.S.), with non-small cell lung cancer (NSCLC) accounting for approximately 80-85% of cases. [1-3] Around 70% of patients with lung cancer are already in advanced or metastatic stages at diagnosis, with a five-year relative survival rate of only 9%.[137] Immunotherapy has significantly improved survival outcomes in patients with metastatic NSCLC (mNSCLC). Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that block specific proteins in immune cells and cancer cells, thereby enhancing the immune system to recognize and attack cancer cells more effectively.[5] Since March 2015, the Food and Drug Administration (FDA) has approved seven ICIs as first-line treatments for mNSCLC.[6, 7] These ICIs included three programmed death-1 (PD-1) inhibitors: nivolumab, pembrolizumab, and cemiplimab; two programmed death ligand 1 (PD-L1) inhibitors: atezolizumab and durvalumab; and two cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors: ipilimumab and tremelimumab.[6, 7]

Despite ICIs' significant survival benefits, optimal immunotherapy regimens for mNSCLC remain uncertain, especially in the older patient population. Current National Comprehensive Cancer Network (NCCN) guidelines recommend 4 to 6 cycles of chemotherapy combined with immunotherapy (ICI-Chemotherapy) for patients with mNSCLC, irrespective of PD-L1 expression. Additionally, first-line ICI monotherapy (ICI-Monotherapy) is recommended for patients with PD-L1 expression of 50% or higher.[147] To date, no clinical trial has directly compared the efficacy of ICI-Chemotherapy versus (vs) ICI-Monotherapy. Network meta-analyses (NMA) by Wang et al. and Dafni et al. have demonstrated that ICI-Chemotherapy significantly improves objective response rates and progression-free survival (PFS) in patients

with high PD-L1 expression, as well as across all levels of PD-L1 expression, respectively.[65, 66] However, one recently published real-world study found no significant difference in OS or PFS between ICI-Chemotherapy and ICI-Monotherapy for older adults with advanced NSCLC regardless of PD-L1 level.[67] Notably, crossing Kaplan-Meier survival curves in this observational study raised questions about the validity of the signal hazard ratio (HR) in the Cox proportional hazard (CPH) model to capture the temporal variations in treatment effectiveness. Moreover, the utilization of concurrent chemotherapy in real-world settings often deviates significantly from controlled clinical environments. This variation may limit the ability of intention-to-treat (ITT) study designs to fully capture the treatment effects as specified by the NCCN guidelines. Considering these methodological challenges and potential biases in existing evidence, we conducted an emulated target trial using population-based data to compare OS between first-line ICI-Chemotherapy vs ICI-Monotherapy in ITT and per-protocol (PP) analysis. Additionally, the NCCN guidance regarding the duration of chemotherapy within ICI-Chemotherapy regimens suggests a range of 4 to 6 cycles.[147] However, uncertainties persist regarding the necessity and benefit of continuing chemotherapy beyond the initial 4 cycles. Therefore, we conducted a secondary target trial to evaluate the OS of patients initiating ICI-Chemotherapy who received 4 cycles of chemotherapy compared to those who completed 6 cycles.

Methods

Study Data: SEER–Medicare Linked Database

This retrospective cohort study utilized the Surveillance, Epidemiology, and End Results (SEER)–Medicare linked database from January 1, 2014, to December 31, 2020, to compare OS among patients with mNSCLC who received first-line ICI-Monotherapy vs ICI-Chemotherapy.

SEER is the largest population-based cancer registry data in the U.S., covering approximately 48% of the U.S. cancer cases and providing detailed information on patient demographics, tumor characteristics, and follow-up data.[148] Medicare claims provide comprehensive health coverage for adults aged 65 and older, as well as patients under 65 who received social security disability insurance or were diagnosed with end-stage renal disease in the U.S.[140] The linkage of SEER and Medicare data enables robust epidemiological research on cancer treatment and outcomes.[87]

Given that nivolumab was marketed as the first ICI treatment for mNSCLC on March 4, 2015, we included SEER cancer registry data from January 1, 2015, to December 31, 2019, and linked Medicare enrollment and claims data from January 1, 2014, to December 31, 2020.[8] We identified eligible patients, treatment utilization, and other relevant variables using SEER, Medicare beneficiary enrollment data, inpatient hospital care, national claims history, outpatient services, Home Health Agencies, hospice care, and durable medical equipment records. The institutional review board at the authors' institution approved this study and deemed it exempt from full review.

Emulating Target Trials in the SEER–Medicare Linked Database

Our approach involved two key steps. First, we specified the protocol for two hypothetical target trials: (1) first-line ICI-Monotherapy vs ICI-Chemotherapy, and (2) 4 vs 6 cycles of Chemotherapy among patients receiving first-line ICI-Chemotherapy. The hypothetical target trials were designed based on existing randomized trials, real-world evidence of treatment utilization, and oncology clinicians' recommendations.[100-103] Second, we emulated target trials using the SEER-Medicare data. The specifications of the target trials and the emulation procedure are summarized in **Table 1** and **Table 2**.

Eligibility Criteria

This study included patients diagnosed with mNSCLC between January 1, 2015, and December 31, 2019, treated with first-line ICI-Monotherapy or ICI-Chemotherapy. The International Classification of Diseases for Oncology, third edition (ICD-O-3) codes were used to identify patients with mNSCLC in the SEER database (**Supplementary Table 1**).[88-91]

The inclusion criteria were: (1) patients aged 66 years or older at the time of mNSCLC diagnosis, (2) initiation of first-line ICI treatment within six months of mNSCLC diagnosis, and (3) continuous enrollment in Medicare Part A and Part B from six months prior to diagnosis through the initiation of ICI treatment. ICIs and chemotherapy were identified from Medicare Part B claims using Healthcare Common Procedural Coding System (HCPCS) codes. First-line treatment was defined as the initial cancer treatment administered following diagnosis. The exclusion criteria were: (1) Medicare beneficiaries who received ICIs, chemotherapy, or radiation within six months prior to their metastatic cancer diagnosis, (2) those who received chemotherapy or radiation after diagnosis and before ICI initiation, and (3) those who initiated first-line treatment more than six months after diagnosis.[92]

Treatment Strategies and Assignment

In the first hypothetical target trial, eligible individuals were randomly assigned to receive ICI-Chemotherapy or ICI-Monotherapy. Chemotherapy utilization for each cycle was identified using a 3-week (21-day) interval, consistent with clinical trial protocols.[101-103] In the second target trial, patients who initiated first-line ICI-Chemotherapy and completed at least 4 cycles of chemotherapy were assigned to either continue chemotherapy to 6 cycles or stop after 4 cycles. Observational analyses were designed to emulate randomized treatment assignments and

treatment adherence by adjusting for potential baseline and time-varying confounders. At baseline, we accounted for demographic characteristics (age, sex, race, metropolitan status, geographic region, year of cancer diagnosis, and the Yost Index of socioeconomic status) as well as clinical factors (tumor histology, concurrent radiation during first-line treatment, modified Charlson Comorbidity Index (CCI) excluding cancer, and the time from cancer diagnosis to the initiation of ICI treatment).[104] Patient characteristics and NSCLC histology were assessed at the time of diagnosis. Modified CCI was calculated using Medicare claims data from the six months before the ICI initiation.[105, 106] To account for evolving prognostic factors and changes in treatment patterns, we incorporated time-varying covariates updated every 21 days (3 weeks), including ICI adherence, emergency department visits, updated CCI, and adverse events including pneumonitis, diarrhea, hypothyroidism, and acute kidney injury (AKI).[105, 106] Emergency department visits and adverse events were identified using HCPCS and ICD-9/10 codes (**Supplementary Table 1**).

Outcomes, Time Zero, and Follow-up

The primary outcome was OS (all-cause mortality). We used the Medicare date of death, which is validated against the National Death Index.[107] Follow-up began on the date of first-line ICI initiation (time zero) and ended at the earliest occurrence of one of the following events: (1) death; (2) loss of Medicare Part A or B enrollment; (3) the administrative cutoff date of December 31, 2020; or (4) completion of a 72-week follow-up period. In the second target trial, only patients who initiated first-line ICI-Chemotherapy and adhered to four cycles of chemotherapy were included. For this trial, time zero was defined as the end of the fourth cycle of ICI-Chemotherapy. The maximum follow-up duration was limited to 60 weeks since the first 12-week (four cycles) observation period was required to assess eligibility for inclusion.

Causal Contrast

Our causal contrasts of interest were the modified ITT and PP effects. In the first target trial, the modified intention-to-treat effect is the effect of ICI-Chemotherapy initiation vs ICI-Monotherapy initiation (the intention-to-treat effect would be the effect of assignment to one of these strategies).[108] In contrast, the PP effect evaluates the treatment effect among patients who strictly adhered to the protocol. For the PP effect in the first trial, patients assigned to ICI-Chemotherapy who discontinued chemotherapy within 4 cycles and those assigned to ICI-Monotherapy who subsequently received ICI-Chemotherapy were censored at the point of deviation. In the second trial, patients assigned to a 4-cycle regimen who received additional chemotherapy within the next two cycles were censored at such cycle, and those assigned to 6 cycles who did not receive chemotherapy at the fifth or 6 cycle were censored at that time.

Statistical Analysis

Patient characteristics were summarized descriptively, and chemotherapy utilization was visualized by plotting the proportion of patients receiving chemotherapy at each treatment cycle. We employed a clone-censor-weight approach to address immortal time bias because patients receiving chemotherapy might inherently survive longer.[109] Initially, all patients who initiated first-line ICIs were duplicated (cloned) and assigned to both ICI-Chemotherapy and ICI-Monotherapy groups. Under the modified ITT analysis, patients assigned to ICI-Monotherapy who received chemotherapy in cycle 1 and those assigned to ICI-Chemotherapy who did not receive chemotherapy in cycle 1 were right censored at cycle 1. For the PP analysis, patients in the ICI-Chemotherapy group who discontinued chemotherapy within the first 4 cycles and those in the ICI-Monotherapy group who initiated ICI-Chemotherapy during the whole follow-up time were censored at the time of deviation.[101-103]

We applied stabilized inverse probability of censoring weights (sIPCW) to construct a pseudopopulation in which time-varying prognostic factors were independent of deviations from the assigned treatment.[110] To derive sIPCW, we first fitted a numerator model using pooled logistic regression that included the assigned treatment groups, time (modeled as cycles using four-knot restricted cubic splines), interaction terms between assigned treatment groups and time, and all baseline covariates. The denominator model had the same core specifications but additionally incorporated one-cycle lagged values of the time-varying covariates.

$$sIPCW_t = \prod_{K=1}^{t} \frac{f(C_t = 0 |\, V_0, C_{t-1} = 0)}{f(C_t = 0 | V_0, L_{t-1}, C_{t-1} = 0)}$$

Here, $C_t = 0$ indicated the individual remained uncensored at time *t*. V_0 represented baseline covariates, L_{t-1} represented the one-cycle lagged time-varying covariates updated in each cycle. Stabilized weights were calculated as the cumulative product of the predicted probabilities from the numerator model divided by those from the denominator model.

Next, we applied a weighted discrete-time hazard model via pooled logistic regression to model the probability of death at each cycle. The model included treatment strategy (ICI-Chemotherapy vs ICI-Monotherapy), time (modeled as cycles using restricted cubic splines), interaction terms between treatment groups and time, and all baseline covariates. We standardized the model-based estimates to the joint distribution of baseline characteristics to obtain adjusted, treatment-specific risks per cycle. Specifically, using the fitted model coefficients and a 'cloned' population with identical baseline covariate distributions across both groups, we calculated survival probabilities for each cycle and generated the survival curves. Additionally, we reported 72-week survival probabilities along with corresponding 95% confidence intervals (CIs) based on 300 nonparametric bootstrap resamples. We also estimated

the 72-week restricted mean survival time (RMST), the RMST difference, and the hazard ratio (HR) using RMST and Cox proportional hazards (CPH) models. The 95% CIs of RMST difference and HR were also generated from 300 resample nonparametric bootstraps.

In the second target trial, we examined the PP effect of receiving 4 vs 6 chemotherapy cycles among patients already on first-line ICI-Chemotherapy. Patients who initiated first-line ICI-Chemotherapy and completed 4 cycles of chemotherapy were identified, then "cloned" and assigned to either a 4-cycle or a 6-cycle chemotherapy strategy. In the 4-cycle group, individuals continuing chemotherapy beyond 4 cycles were censored at that point, while in the 6-cycle group, those discontinuing chemotherapy prior to 6 cycles were censored. After applying sIPCW to mitigate selection bias, we used weighted outcome regression to estimate survival probabilities, RMST differences, and HRs standardized to baseline characteristics, as described above.

One limitation of our analysis was the definition of a treatment cycle. Although clinical trials often define chemotherapy cycles as 21 days, real-world practice may involve longer intervals. Following a literature review and consultation with clinicians, we adopted a 28-day (4 weeks) cycle length to reflect real-world chemotherapy administration patterns and accommodate time-varying covariates in a sensitivity analysis.[101-103, 111] In this sensitivity analysis, we extended the maximum follow-up time to 96 weeks for the comparison between ICI-Chemotherapy and ICI-Monotherapy (corresponding to 24 cycles of 4-week intervals), and to 80 weeks for the comparison of 4 vs 6 cycles of chemotherapy in the second target trial. Data processing was performed using SAS version 9.4 (SAS Institute Inc.), and analyses were conducted using R version 4.4.1 (R Foundation). A two-tailed Type I error rate of 5% was used to determine statistical significance.

Results

Patient characteristics

A total of 3,981 patients with mNSCLC were included, comprising 2,057 (51.7%) who received ICI-Monotherapy and 1,924 (48.3%) who received ICI-Chemotherapy. The median age with 95% CI was 78 (66-91) years in the ICI-Monotherapy group and 74 (66-86) years in the ICI-Chemotherapy group. The median time from cancer diagnosis to treatment initiation was 58 (22-159) days in the ICI-Monotherapy group and 55 (20-138) days in the ICI-Chemotherapy group. Both groups had similar comorbidity burdens, with a median CCI of 2 (0-7). Pembrolizumab was the predominant ICI used in both groups (88.6% in ICI-Monotherapy and 95.1% in ICI-Chemotherapy), followed by nivolumab (10.6%) and atezolizumab (0.8%) in the ICI-Monotherapy group, as well as atezolizumab (4.3%) and nivolumab (0.6%) in the ICI-Chemotherapy group. Patients were diagnosed predominantly in 2018 and 2019, with a larger proportion diagnosed in 2019 in the ICI-Chemotherapy group (51.8%) compared with the ICI-Monotherapy group (27.5%). Geographic distribution was similar between groups, with 86.6% of patients in the ICI-monotherapy group and 83.6% in the ICI-chemotherapy group residing in metropolitan areas. Women accounted for 50.9% of the ICI-Monotherapy group and 43.4% of the ICI-Chemotherapy group. White patients were the majority in both groups (91.1% in ICI-Monotherapy and 89.2% in ICI-Chemotherapy). Nonsquamous histology was more common than squamous in both cohorts (78.6% vs 21.4% in ICI-Monotherapy; 81.9% vs 18.1% in ICI-Chemotherapy). Fewer than 10% of patients in either group received radiation therapy during the first-line ICI treatment (9.3% in ICI-Monotherapy and 8.5% in ICI-Chemotherapy). Within the ICI-Chemotherapy group, carboplatin plus pemetrexed (70.8%) and carboplatin plus paclitaxel (22.1%) were the most common regimens. Baseline time-varying covariates, including

pneumonitis, hypothyroidism, diarrhea, and AKI, were comparable between the two groups (**Supplementary Table 2**). In the second target trial, a total of 830 patients were included, with 318 (38.3%) receiving 4 cycles of chemotherapy and 512 (61.7%) receiving more than 4 cycles of chemotherapy. Patient characteristics are summarized in **Supplementary Table 3**.

Chemotherapy Utilization

Chemotherapy utilization is shown in **Supplementary Figure 2**. Among patients who initiated ICI-Chemotherapy, chemotherapy utilization decreased with each cycle (76.2% at cycle 2, 71.4% at cycle 3, 65.2% at cycle 4, and 42.1% at cycle 6). In contrast, chemotherapy use in the ICI-Monotherapy group gradually increased from 0% to 7.1% by cycle 6.

Overall Survival

The main results of the comparative OS are presented in **Table 3 and Figure 1-3**. At 72 weeks, the modified ITT analysis showed similar survival rates between ICI-Monotherapy and ICI-Chemotherapy (39.0% vs 39.7%; survival rate difference=0.7%; 95% CI: -0.5% to 1.9%). However, ICI-Chemotherapy was associated with a 2.9-week longer RMST (95% CI: 1.50-4.17) and a significantly lower hazard of death (HR=0.86, 95% CI, 0.81-0.91) compared with ICI-Monotherapy. Under the PP analysis, the OS benefits of ICI-Chemotherapy were more pronounced: ICI-Chemotherapy improved the survival rate by 5.5% (95% CI: 4.2%-6.7%), extended RMST by 6.27 weeks (95% CI: 4.88-7.61), and yielded a hazard ratio of 0.76 (0.71-0.81) compared to ICI-Monotherapy. When comparing patients receiving 4 vs 6 cycles of chemotherapy in the second target trial, those completing 6 cycles experienced modestly improved OS outcomes in 72 weeks, including a 5.1% improvement in survival rate at week 72

(95% CI: -0.9% to 11.0%), an additional 2.19 weeks RMST gain (95% CI: 0.54-4.92), and an HR of 0.83 (95% CI: 0.65-0.95) compared to 4 cycles of chemotherapy.

In sensitivity analysis, chemotherapy utilization was captured in 4-week cycles. The modified ITT analysis shows negligible differences in overall survival rates at 96 weeks (32.3% vs 32.5%, survival difference -0.2%, 95% CI: -1.3% to 0.9%), but significant RMST and HR benefits for ICI-Chemotherapy (RMST difference=2.84, 95% CI, 1.31-4.57; HR=0.89, 95% CI, 0.85-0.93) (**Table 4, Supplementary Figure 3-5**). PP analyses showed that the additional chemotherapy improved a 2.7% survival rate (95% CI: 1.4%-4.1%), extended RMST by 6.00 weeks (95% CI, 4.52-8.08), and produced an HR of 0.83 (95% CI, 0.78-0.87). Similarly, among patients receiving 4 vs 6 cycles of chemotherapy, those receiving 6 cycles had a 5.6% higher 96-week survival rate (95% CI: 0.0%-11.7%). The 2.16-week RMST increase (95% CI, -0.64 to 6.08) and HR of 0.88 (95% CI, 0.74-1.03) did not reach statistical significance.

Discussion

In this population-based emulation of target trials among older adults with mNSCLC, first-line ICI-Chemotherapy was associated with modest but consistent improvement in OS compared with ICI-Monotherapy. Although the modified ITT analyses at 72 weeks demonstrated a similar OS rate, both RMST and HRs showed a significant survival benefit of ICI-Chemotherapy compared to ICI-Monotherapy. PP analyses revealed more pronounced OS gains with ICI-Chemotherapy, including higher survival rates, longer RMSTs, and lower hazards of death in both the primary and sensitivity analyses. The second target trial provided further insight into the optimal duration of chemotherapy when combined with ICIs. Patients continuing chemotherapy after 4 to 6 cycles achieved significant improvement in 72-week survival, RMST, and HRs compared with those who stopped at four cycles in the main analysis. Although these benefits did

not reach statistical significance for RMST and hazard ratios in the sensitivity analysis, the upper bound of the CIs was close to 1, and the 24-cycle survival rate remained significantly higher in the 6-cycle group.

These findings provide valuable insight into the ongoing evolution of evidence-based first-line ICI treatment regimens. Although NMA of clinical trial results have indicated superior OS with ICI-Chemotherapy, definitive OS benefits and the optimal duration of chemotherapy remain unclear in older adults who are often underrepresented in randomized clinical trials.[65, 66] Notably, our results differ from prior observational studies for several reasons.[67] First, the NCCN guidelines recommend 4 to 6 cycles of chemotherapy, which may not substantially affect long-term survival. Consequently, we limited our follow-up to 72 weeks rather than 36 months to focus on a shorter time frame where OS differences are more likely to be directly relevant to treatment decisions. Second, we observed a dramatic decline in chemotherapy use among patients initiated on ICI-Chemotherapy, decreasing from 76.2% at cycle 2 to 65.2% at cycle 4. Such early discontinuation may obscure the estimation of the treatment effect in modified ITT analysis based on real-world data. Indeed, our modified ITT analysis showed a similar survival rate at 72 weeks between the two groups, which was consistent with a previous observational study showing overlapping Kaplan-Meier curves around 14 to 20 months.[67] Our study provides insights into the treatment benefits of ICI-Chemotherapy in relatively validated follow-up time, and the PP findings support the evidence that adhering to 4 cycles of chemotherapy yields improved OS. On the other hand, a real-world cohort study identified that the survival outcomes among older adults with advanced NSCLC receiving first-line ICIs are much shorter than those observed in registrational trials.[149] Specifically, when compared to chemotherapy, first-line pembrolizumab monotherapy did not improve OS, with an RMST difference of -0.2 months

(95% CI, –0.5 to 0.2; $p = .30$). In contrast, pembrolizumab combined with chemotherapy was associated with a modest survival benefit, yielding an RMST difference of 0.5 months (95% CI, 0.1 to 0.9; $p = .02$) compared to chemotherapy.[149] Our study further supported the OS benefit of first-line ICI-Chemotherapy by directly comparing it to ICI-Monotherapy in Medicare beneficiaries.

We also evaluated whether continuing chemotherapy beyond 4 cycles to 6 cycles provides additional OS benefits, as some clinicians opt for maintenance therapy if patients have not experienced disease progression by this point.[147] To the best of our knowledge, reliable evidence on the optimal duration of chemotherapy is lacking. Our results suggest that extending chemotherapy beyond 4 to 6 cycles may offer modest OS advantages. In sensitivity analyses, the upper bounds of the HR slightly exceeded 1, potentially influenced by the smaller sample size in the second target trial. These findings identified the potential benefits of prolonged chemotherapy to 6 cycles in ICI-Chemotherapy regimens and highlighted the need for prospective observational studies to establish the long-term effectiveness and safety of additional chemotherapy in older adults with mNSCLC.

However, this study has limitations. The SEER-Medicare database lacks key clinical details, including PD-L1 expression, cancer progression, and molecular profiles, which are essential for optimizing chemotherapy selection in first-line ICI regimens and prognostication. The absence of these variables introduces residual confounding and potential bias in the observed treatment effects. Secondly, since the indications for ICI regimens vary by PD-L1 expression level, ICI-Chemotherapy regimens also warrant further evaluation and comparison with ICI-Monotherapy, stratified by the PD-L1 expression. In addition, coding inaccuracies and variability in clinical practice and administrative claims may affect how treatments and outcomes

are captured, potentially leading to measurement bias. Finally, our cohort was limited to Medicare beneficiaries, which could restrict the generalizability of these findings to younger or uninsured populations.

In conclusion, our results demonstrate that ICI-Chemotherapy provides significant survival advantages compared with ICI-Monotherapy in older adults with mNSCLC. In addition, extending chemotherapy beyond 4 cycles may further improve OS outcomes. These findings can inform clinical decision-making in highlighting the benefit of chemotherapy as a component of first-line ICI regimens in the Medicare population. Moving forward, additional observational studies and clinical trials are warranted to incorporate a broader range of prognostic variables, assess the safety of prolonged chemotherapy, and refine treatment duration strategies to optimize survival outcomes with ICI-based regimens in real-world oncology settings.

Figure 1. Survival curves from the intention-to-treat analysis of the emulated target trial comparing first-line ICI–Chemotherapy vs. ICI–Monotherapy in metastatic non–small cell lung cancer

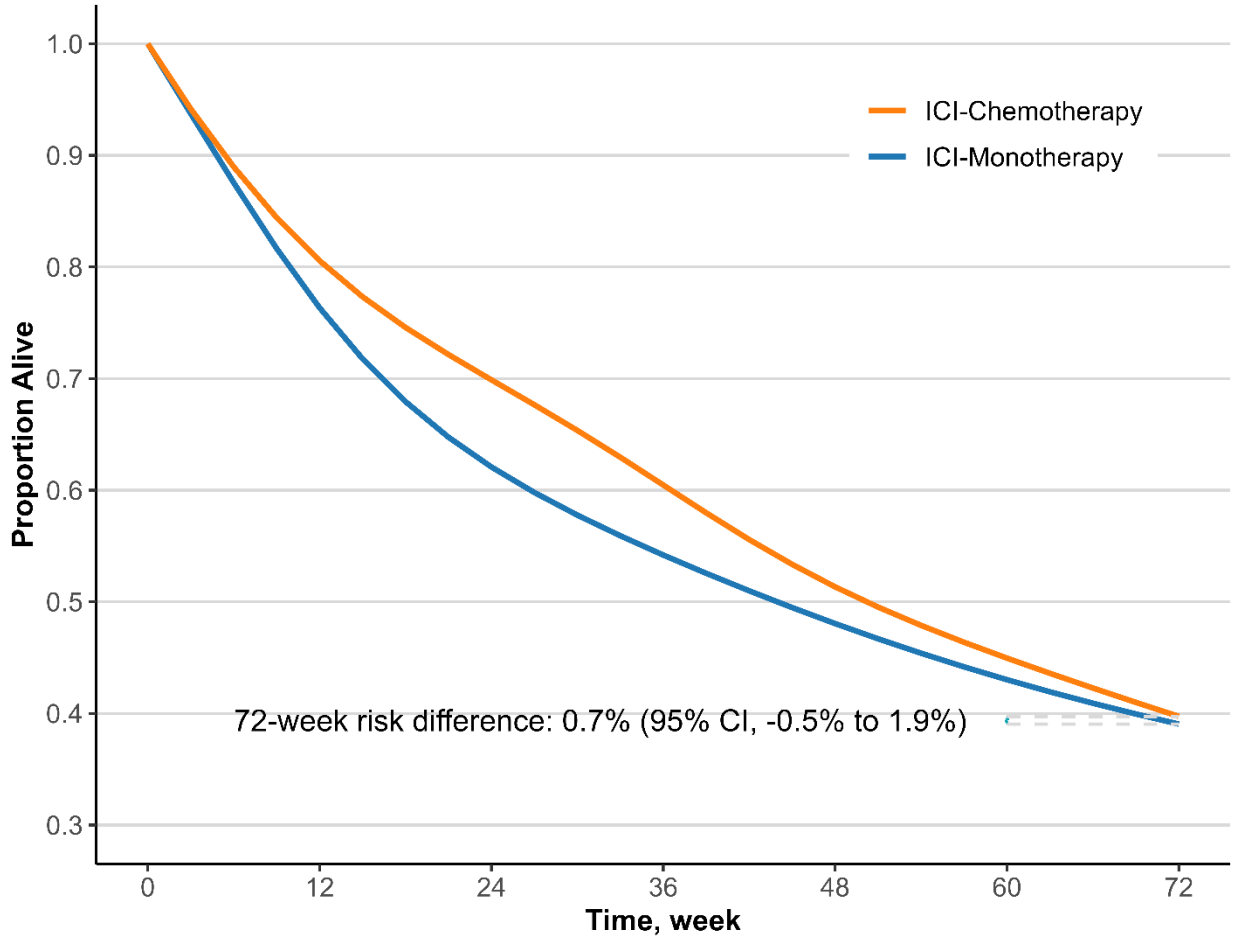


Figure 2. Survival curves from the per-protocol analysis of the emulated target trial of first-line ICI-Chemotherapy vs. ICI-Monotherapy in metastatic non-small cell lung cancer

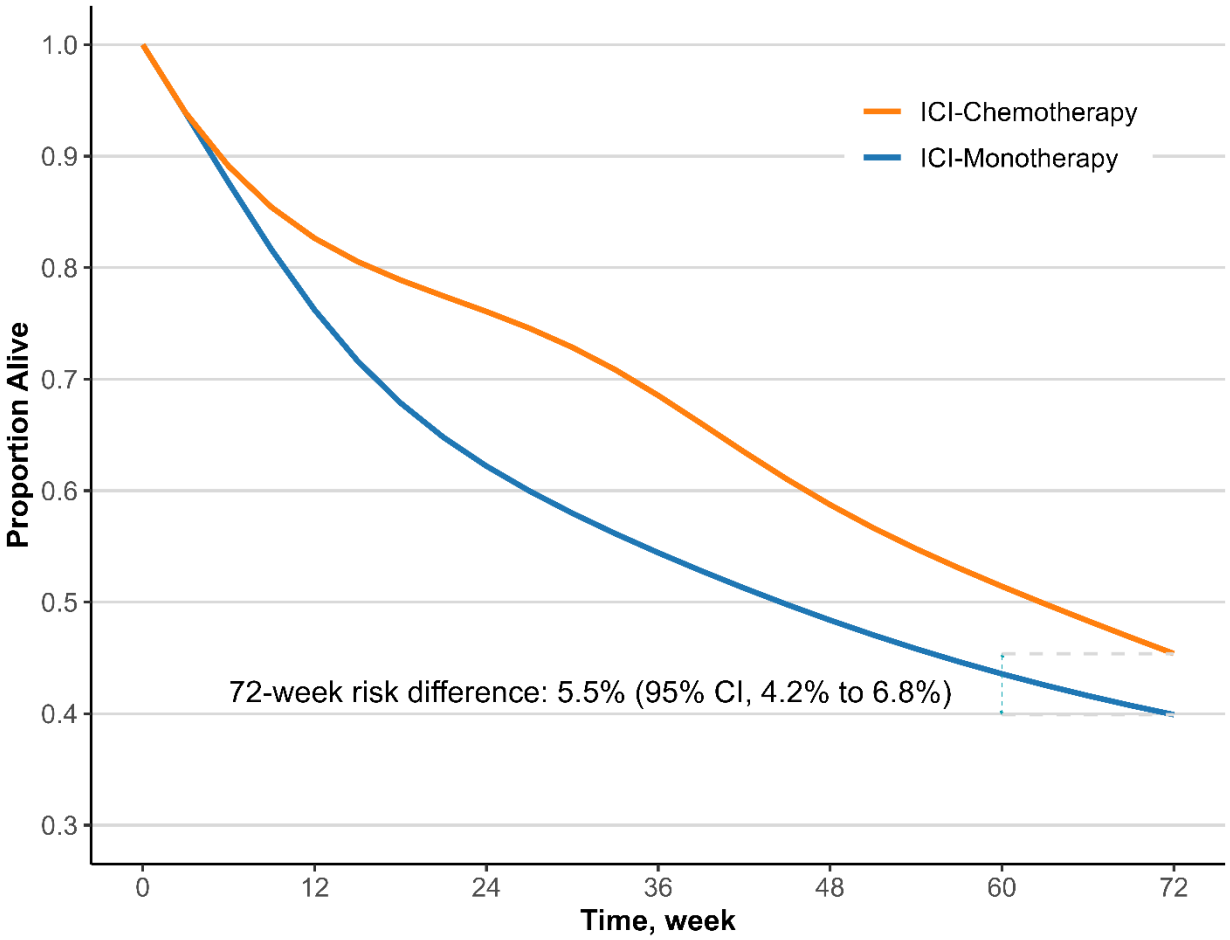


Figure 3. Survival curves from the per-protocol analysis of the emulated target trial comparing 4-cycle vs. 6-cycle chemotherapy in the first-line ICI–Chemotherapy regimen for metastatic non–small cell lung cancer

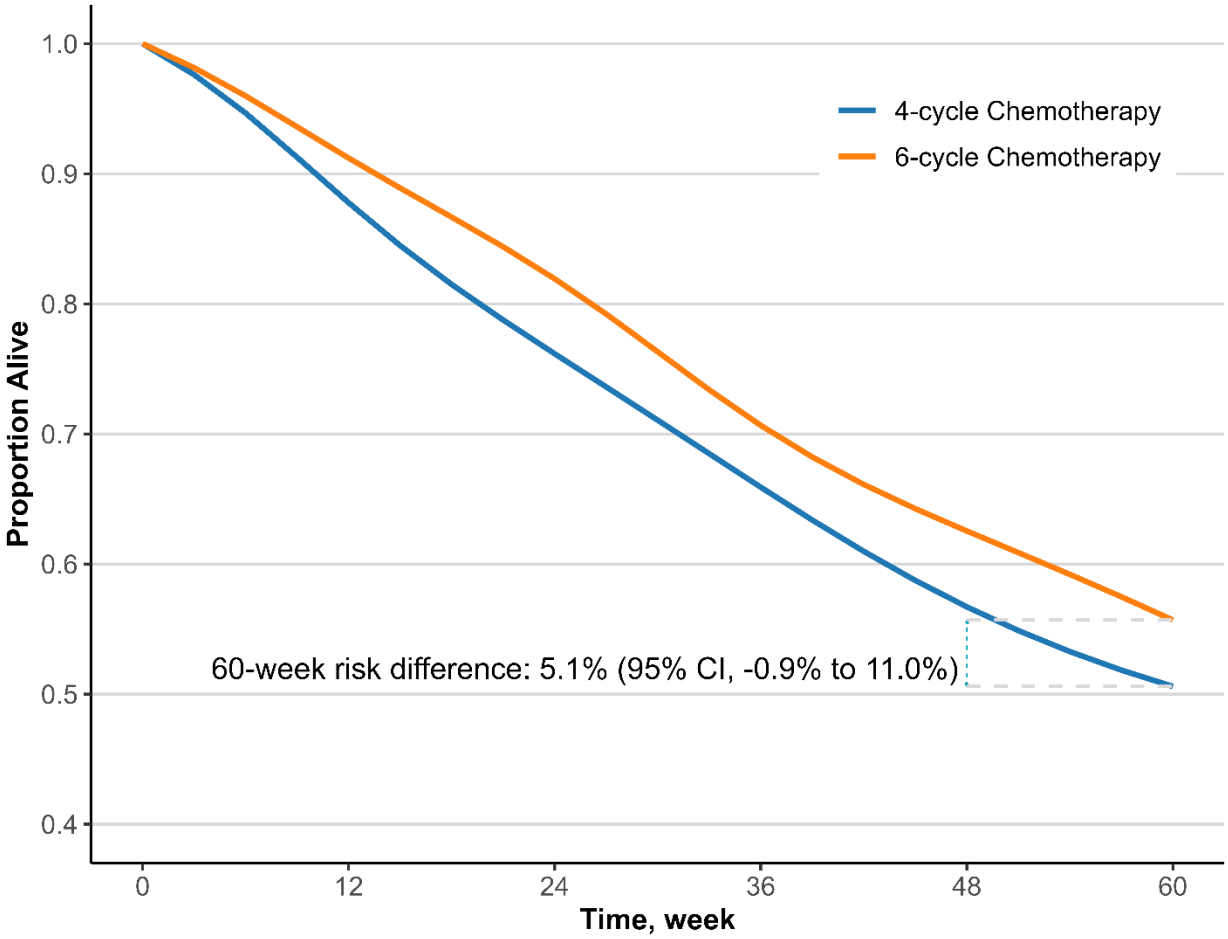


Table 1. Protocol of the target trial to evaluate the addition of chemotherapy to first-line immunotherapy in metastatic non-small cell lung cancer and emulation procedure using the SEER-Medicare database

Protocol Component	Description of Target Trial	Emulation Using SEER-Medicare Data
Eligibility	• Diagnosis of mNSCLC between Jan 01, 2015, and Dec 31, 2019 • Aged 66 or older at diagnosis, continuously enrolled in Medicare Parts A and B six months prior to diagnosis through the initiation of first-line treatment • Initiation of first-line ICI-Monotherapy or ICI-Chemotherapy within 6 months of diagnosis • No prior ICI, chemotherapy, or radiation treatment six months before diagnosis	Same as the target trial.
Treatment Strategies	• First-line ICI-Chemotherapy with continuous use of chemotherapy for at least four cycles • First-line ICI-monotherapy	Same as the target trial.
Assignment Procedures	Participants randomized to receive either ICI-Chemotherapy or ICI monotherapy	Randomization was assumed conditional on baseline covariates: age, sex, race, metropolitan status, geographic region, socioeconomic status, year of diagnosis, histology, first-line radiation, time from diagnosis to the treatment initiation, CCI[#], pre-treatment emergency department visits*, pneumonitis*, diarrhea*, hypothyroidism*, and acute kidney injury*.
Follow-up	Follow-up begins at the initiation of first-line treatment and ends at the earliest of death, loss of insurance eligibility, December 31, 2020, or 72 weeks	Same as the target trial
Outcome	Death confirmed by National Death Index in Medicare claims	Same as the target trial

Causal Contrast	Intention-to-treat effect, per-protocol effect	Modified intention-to-treat effect: the effect of ICI-Chemotherapy initiation vs ICI-Monotherapy initiation, per-protocol effect
Analysis Plan	Intention-to-treat analysis; Per-protocol analysis: Stabilized IPCW with censoring at deviation from protocol. Weights are estimated as a function of baseline and time-varying covariates, including emergency department visits, ICI utilization, CCI, pneumonitis, diarrhea, hypothyroidism, and acute kidney injury	Same as the target trial

Identification based on six months before first-line ICI initiation (Index date)
* Identification based on the 21 days before the Index date

Table 2. Protocol of the target trial to evaluate the 4 cycles of chemotherapy versus 6 cycles of chemotherapy in first-line ICI-Chemotherapy regimen for metastatic non-small cell lung cancer and emulation procedure using the SEER-Medicare database

Protocol Component	Description of Target Trial	Emulation Using SEER-Medicare Data
Eligibility	• Diagnosis of mNSCLC between Jan 01, 2015, and Dec 31, 2019 • Aged 66 or older at diagnosis, continuously enrolled in Medicare Parts A and B six months prior to diagnosis through the initiation of first-line treatment • Initiation of first-line ICI-Chemotherapy within 6 months of diagnosis • No prior ICI, chemotherapy, or radiation treatment six months before diagnosis • Received 4 cycles of chemotherapy after ICI-Chemotherapy initiation	Same as the target trial.
Treatment Strategies	• Four cycles of chemotherapy in ICI-Chemotherapy regimens • Six or more cycles of chemotherapy in ICI-Chemotherapy regimens	Same as the target trial.
Assignment Procedures	Participants were randomized to receive either 4 cycles of chemotherapy or 6 or more cycles of chemotherapy	Randomization was assumed conditional on baseline covariates: age, sex, race, metropolitan status, geographic region, socioeconomic status, year of diagnosis, histology, first-line radiation, time from diagnosis to the treatment initiation, CCI[#], pre-treatment emergency department visits*, pneumonitis*, diarrhea*, hypothyroidism*, and acute kidney injury*, ICI utilization at four-cycle*.
Follow-up	Follow-up begins at the initiation of first-line treatment and ends at the earliest of death, loss of insurance eligibility, December 31, 2020, or 72 weeks	Same as the target trial

Outcome	Death confirmed by National Death Index in Medicare claims	Same as the target trial
Causal Contrast	Per-protocol effect	Same as the target trial
Analysis Plan	Intention-to-treat analysis; Per-protocol analysis: Stabilized IPCW with censoring at deviation from protocol. Weights are estimated as a function of baseline and time-varying covariates, including emergency department visits, ICI utilization, CCI, pneumonitis, diarrhea, hypothyroidism, and acute kidney injury	Same as the target trial

Identification based on six months before first-line ICI initiation (Index date)
* Identification based on the 21 days before the Index date

Table 3. 72-week survival rate, restricted mean survival time, and hazard ratios comparing first-line ICI-Monotherapy vs. ICI-Chemotherapy, and 4 vs. 6 cycles of chemotherapy in first-line ICI-chemotherapy

	72-week survival rate, %	72-week survival difference, % (95% CI)	72-week RMST, weeks	72-week RMST difference, weeks (95% CI)	Hazard Ratio (95% CI)
Intention to treat analysis					
ICI-Monotherapy	39.0	Reference	43.35	Reference	Reference
ICI-Chemotherapy	40.7	0.7 (-0.5, 1.9)	46.23	2.88 (1.50, 4.17)	0.86 (0.81, 0.91)
Per-protocol analysis					
ICI-Monotherapy	39.9	Reference	44.7	Reference	Reference
ICI-Chemotherapy	45.4	5.5 (4.2, 6.7)	51.0	6.27 (4.88, 7.61)	0.76 (0.71, 0.81)
Per-protocol analysis (4 cycles of chemotherapy versus 6 or more cycles of chemotherapy) *					
4-cycles	50.6	Reference	45.84^	Reference	Reference
6-cycles	55.7	5.1 (-0.9, 11.0)	48.03^	2.19 (0.54, 4.92)	0.83 (0.65, 0.95)

OS = overall survival; CI = confidence interval; RMST = restricted mean survival time.
In the first target trial, 2,057 patients received ICI-Monotherapy and 1,924 patients received ICI-Chemotherapy. In the second target trial, 318 patients completed four cycles of chemotherapy, and 512 continued chemotherapy after four cycles.
* The index day is the end of 4 weeks (4-cycle) after first-line immune checkpoint inhibitor initiation
^ The restricted mean survival time does not include the first 4 weeks of ICI-Chemotherapy

Table 4. 96-week survival rate, restricted mean survival time, and hazard ratios comparing first-line ICI-Monotherapy vs. ICI-Chemotherapy, and 4 vs. 6 cycles of chemotherapy in first-line ICI-Chemotherapy

	96-week survival rate, %	96-week survival difference, % (95% CI)	96-week RMST, weeks	96-week RMST difference, weeks (95% CI)	Hazard ratio (95% CI)
Intention to treat analysis					
ICI-Monotherapy	32.5	Reference	54.18	Reference	Reference
ICI-Chemotherapy	32.3	-0.2 (-1.3, 0.9)	57.02	2.84 (1.31, 4.57)	0.89 (0.85, 0.93)
Per-protocol analysis					
ICI-Monotherapy	34.0	Reference	54.72	Reference	Reference
ICI-Chemotherapy	36.7	2.7 (1.4, 4.1)	60.68	6.00 (4.52, 8.08)	0.83 (0.78, 0.87)
Per-protocol analysis (4 cycles of chemotherapy versus 6 or more cycles of chemotherapy) *					
4-cycles	40.7	Reference	54.16^	Reference	Reference
6-cycles	46.3	5.6 (0.0, 11.7)	56.32^	2.16 (-0.64, 6.08)	0.88 (0.74, 1.03)

OS: overall survival; CI: confidence interval; RMST: restricted mean survival time.
In the first target trial, 2,057 patients received ICI-Monotherapy and 1,924 patients received ICI-Chemotherapy. In the second target trial, 301 patients completed four cycles of chemotherapy, and 503 continued chemotherapy after four cycles.
* The index day is the end of 4 weeks (4-cycle) after first-line immune checkpoint inhibitor initiation
^ The restricted mean survival time does not include the first 4 weeks of ICI-Chemotherapy

Aim 2 Manuscript

We systematically examined the 3-month incidence of irAEs in patients with mNSCLC initiating first-line ICIs (Table 14). We then conducted exploratory analyses using LASSO regression and RF models to predict the occurrence of irAEs, pneumonitis, and gastrointestinal irAEs within the same time frame (Table 15). Based on the AUROC, the models demonstrated suboptimal performance for these outcomes (AUROC< 0.7). Consequently, we explored other types of irAEs and observed improved model performance when focusing on endocrine-related events. As a result, we refined Aim 2 analyses and the manuscript to focus on endocrine-related irAEs as the primary outcome of interest.

Table 14. Frequency of immune-related adverse events

Category	Disease	N (%)
Dermatologic	Eruption	25 (0.6%)
	Pruritus	166 (3.9%)
	Lichen_Planus	-
	Vitiligo	26 (0.6%)
	Bullous_Pemphigoid	11 (0.3%)
	SJS_TEN	-
Hematologic	Anemia	799 (19%)
	Thrombocytopenia	122 (2.9%)
	Leukopenia	426 (10%)
Pulmonary	Pneumonitis	1380 (33%)
Liver	Hepatitis	372 (8.8%)
Gastrointestinal	Diarrhea	624 (15%)
	Colitis	243 (5.8%)
	Pancreatitis	32 (0.8%)
	Mucositis	76 (1.8%)
Endocrine	Hypothyroidism	1053 (25%)
	Hyperthyroidism	108 (2.6%)
	Diabetes_Type_I	138 (3.3%)
	DKA	13 (0.3%)
	Hypophysitis	14 (0.3%)
	Adrenal_Insufficiency	79 (1.9%)
	Cushing_Syndrome	-
	Hypopituitarism	11 (0.3%)
	Thyroiditis	28 (0.7%)

Category	Disease	N (%)
Renal	Acute Kidney Injury	728 (17%)
	Interstitial_Nephritis	45 (1.1%)
	Glomerulonephritis	17 (0.4%)
Cardiac	Arrhythmia	1186 (28%)
	MI	268 (6.3%)
	Myocarditis	145 (3.4%)
	Pericarditis	98 (2.3%)
	Cardiomyopathy	184 (4.4%)
Musculoskeletal	Dermatopolymyositis	-
	Rheumatoid Arthritis	123 (2.9%)
	Myalgia	134 (3.2%)
	Polymyalgia Rheumatica/Giant Cell Arteritis	11 (0.3%)
CNS	Neuritis/Neuralgia	49 (1.2%)
	Meningitis	-
	Encephalitis	52 (1.2%)
	GBS	-
	Myasthenia Gravis	-
	Peripheral_Neuropathy	-

SJS_TEN: Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis; DKA: Diabetic Ketoacidosis; MI: Myocardial Infarction; GBS: Guillain–Barré Syndrome.
Total N = 4,221.
–: suppressed due to cell size < 11

Table 15. Predictive performance of LASSO and random forest models for irAEs, pneumonitis, and gastrointestinal irAEs

Disease	Model	Accuracy	F1 Score	AUROC
irAEs	**LASSO**	0.6145	0.7460	0.6647
	Random Forest	0.5943	0.5043	0.6290
Pneumonitis	**LASSO**	0.5521	0.4585	0.5806
	Random Forest	0.5581	0.6213	0.5950
Gastrointestinal irAEs	**LASSO**	0.5344	0.3165	0.5795
	Random Forest	0.5166	0.6318	0.5503

LASSO: Least absolute shrinkage and selection operator; IrAEs: Immune-related adverse events

Title: Assessing Risk Factors for Endocrine-Related Adverse Events in Older Adults with Metastatic NSCLC Treated with First-Line Immune Checkpoint Inhibitors: A Regression and Machine Learning Approach

Abstract

Introduction:

Immune checkpoint inhibitors (ICIs) have significantly improved survival outcomes for patients with metastatic non-small cell lung cancer (mNSCLC). However, they are also associated with a sustained elevated risk of endocrine-related immune-related adverse events (irAEs). Predicting these endocrine toxicities may enable earlier detection and improved patient outcomes.

Objective:

This study aims to predict the 3-month risk of endocrine-related irAEs and to identify associated risk factors using regression and machine learning (ML) models among older adults with mNSCLC receiving first-line ICI treatment.

Methods:

We conducted a retrospective cohort study using the 2014–2020 SEER-Medicare database, including older adults (aged ⩾66 years) diagnosed with mNSCLC who initiated first-line ICI therapy. Candidate predictors were selected through a literature review and extracted from linked claims and cancer registry data. We developed and validated predictive models using LASSO regression and ML algorithms, including random forest (RF), extreme gradient boosting (XGBoost), and support vector machines (SVM), with an 80/20 train-test split. Feature selection was performed using recursive feature elimination for the ML model to reduce model complexity and minimize overfitting. The data were randomly split into training and testing sets 100 times,

and models were trained using 10-fold cross-validation to ensure robustness. Two sensitivity analyses were conducted: 1) to predict 6-month endocrine-related irAEs and 2) to restrict the cohort to patients without pre-existing endocrine conditions.

Results:

A total of 4,222 patients with mNSCLC who initiated ICIs were included. Of these, 892 (21.1%) developed endocrine-related irAEs within three months of treatment initiation. The LASSO model outperformed other ML models, achieving an accuracy of 0.791 (95% CI: 0.789–0.793), an F1 score of 0.507 (95% CI: 0.502–0.512), and an AUROC of 0.724 (95% CI: 0.719–0.728). The most important predictors included pre-existing endocrine disorders, type 2 diabetes, use of atezolizumab, concurrent chemotherapy, and patient demographics. When limited to patients without pre-existing endocrine conditions, the AUROC of the LASSO model reduced significantly to 0.572 (95% CI: 0.566–0.577).

Conclusion:

Our findings suggest that the LASSO model demonstrated the best performance in predicting endocrine-related irAEs using claims-linked data among patients with mNSCLC treated with first-line ICIs. Pre-existing endocrine conditions are the most influential predictors for endocrine-related irAEs. The model warrants further external validation and could be enhanced using additional data sources. The prediction of endocrine-related irAEs may help clinicians identify high-risk patients and tailor treatment strategies to mitigate the risk of endocrine toxicity.

Introduction

Immune checkpoint inhibitors (ICIs) have significantly improved survival outcomes for patients with advanced cancers. However, their immune-mediated mechanisms lead to a unique profile of toxicities termed immune-related adverse events (irAEs).[46] irAEs substantially affect patient quality of life and treatment outcomes, and lead to discontinuation of treatment and death in rare cases.[46] Endocrine glands, with their rich vascular supply, represent one of the most affected organ systems by ICIs.[150] The incidence of endocrine irAEs reported with the use of ICIs ranges from 5% to 10%, but may vary across different age groups.[151] The median time to onset of endocrine toxicities is 14.5 weeks, with a range of 1.5-130 weeks after ICI initiation.[30] On the other hand, real-world evidence indicates that patients with non-small cell lung cancer (NSCLC) undergoing ICI therapy experience a higher incidence of endocrine irAEs compared to those with other cancers, ranging from 12.9% to 30%.[93, 152]

Machine learning (ML) techniques, particularly supervised methods, are increasingly employed to analyze complex, high-dimensional clinical data and to predict health outcomes, including adverse events (AEs). [27, 153] Although previous studies have explored irAEs using the ML method, they were often limited by small sample sizes, did not focus specifically on patients with metastatic NSCLC (mNSCLC), and tended to examine irAEs broadly rather than focusing on endocrine toxicities.[27, 153] To date, there is limited evidence in the prediction of endocrine irAEs using large-scale claims-linked databases for patients with mNSCLC.

To address this gap, we examined a nationally representative cohort of older adults with mNSCLC receiving first-line ICI therapy. We applied and compared the least absolute shrinkage and selection operator (LASSO) regression and three ML models, including random forest (RF), extreme gradient boosting (XGBoost), and support vector machine (SVM), to predict the 3-

month onset of endocrine irAEs. Our study aims to enhance risk stratification, inform targeted monitoring strategies, and ultimately improve clinical outcomes for patients at increased risk of ICI-induced endocrine toxicity.

Methods

Data Sources

This retrospective cohort study utilized the Surveillance, Epidemiology, and End Results (SEER)–Medicare linked database from January 1, 2014, to December 31, 2020, to identify patients with mNSCLC who received first-line ICI therapy. The SEER program is the largest population-based cancer registry in the United States.[154] It covers approximately 48% of cancer cases and provides detailed information on patient demographics, tumor characteristics, initial treatments, and follow-up data.[154] Medicare claims offer comprehensive health coverage for adults aged 65 and older, as well as for individuals under 65 who receive Social Security Disability Insurance or have end-stage renal disease.[140, 141] Hence, linking SEER and Medicare data enables robust epidemiologic research on cancer treatments and outcomes by integrating detailed cancer registry data with longitudinal claims information.

Study Sample

Patients were eligible if they were aged 66 years or older, diagnosed with mNSCLC between July 1, 2014, and December 31, 2019, and received first-line ICI therapy (pembrolizumab, nivolumab, or atezolizumab) within six months after diagnosis. Given that one cycle of first-line treatment typically spans 21 days, first-line ICI treatment was defined as the initiation of ICIs within 21 days following the start of anticancer therapy (e.g., chemotherapy). [34, 63] MNSCLC was identified using the International Classification of Diseases for Oncology, Third Edition

(ICD-O-3) codes within the SEER database. ICI treatments were confirmed through Medicare claims based on the appropriate Healthcare Common Procedure Coding System (HCPCS) codes (**Supplementary Table 1**). To capture the completeness of clinical and claims data, patients were required to have continuous enrollment in Medicare Parts A and B for at least six months before cancer diagnosis through the initiation of ICI therapy. Patients enrolled in Medicare Advantage plans within six months before cancer diagnosis or those with missing data were excluded from the study. This study was reviewed and received an exempt approval at the authors' institution's Institutional Review Board (IRB).

Feature Selection

We included eight broad classes of variables available in the SEER-Medicare database to predict endocrine irAEs following initiation of ICI therapy: (1) demographic variables included age, residence, sex, and race/ethnicity; (2) socioeconomic status (SES) included household median income, percentage of household with education level below high school, and Yost scores; (3) baseline adjusted Charlson Comorbidity Index (CCI); (4) days from cancer diagnosis to ICI initiation; (5) use of individual ICI agents included pembrolizumab, nivolumab, and atezolizumab; (6) other first-line cancer treatments included chemotherapy and radiation therapy; (7) preexisting endocrine conditions prior to ICI initiation included hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, type 1 diabetes, Cushing's syndrome, hypopituitarism, and thyroiditis; (8) and other preexisting conditions included type 2 diabetes, dermatologic and hematologic disorders, pneumonitis, gastrointestinal disorders, renal disease, cardiovascular disease, liver disease, musculoskeletal disorders, and chronic obstructive pulmonary disease (COPD). These features were selected based on clinical relevance and their availability within SEER-Medicare to support model performance and interpretability.[93, 155]

Patients' demographic and socioeconomic information was obtained from SEER cancer registry data files (**Supplementary Table 1**). Comorbidities and preexisting endocrine conditions were identified using ICD-9 and ICD-10 diagnosis codes recorded in Medicare claims during the six months prior to cancer diagnosis (**Supplementary Table 2**). ICI treatment, chemotherapy, and radiation were captured using HCPCS and ICD-9/ICD-10 procedure codes (**Supplementary Table 1**).

Outcome

The primary outcome was the occurrence of endocrine irAEs within 3 months of ICI initiation.[30] Endocrine irAEs were identified using ICD-9 and ICD-10 diagnosis codes from Medicare claims, including hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, type 1 diabetes, Cushing's syndrome, hypopituitarism, and thyroiditis (**Supplementary Table 2**). Given that the median time to onset is approximately 14.5 weeks, we conducted the sensitivity analysis 1 by predicting the occurrence of endocrine irAEs within 6 months.[30] In sensitivity analysis 2, we excluded the patients who had pre-existing endocrine conditions within six months prior to cancer diagnosis to identify risk factors with newly developed endocrine toxicity following ICI treatment.

Model Training and Performance Evaluation

The SEER-Medicare dataset was randomly split at the patient level into training (80%) and test (20%) sets. The test set was used exclusively to evaluate model performance. We developed predictive models using LASSO logistic regression and three ML algorithms: RF, XGBoost, and SVM with a radial basis function kernel. Each model was trained using tenfold cross-validation to enhance predictive accuracy and reduce variability (**Figure 1**).

To reduce overfitting and improve reproducibility, we included only the most relevant features for predicting endocrine irAEs. LASSO logistic regression applies an L1 penalty, inherently performs both feature selection and regularization.[116, 117] For RF, SVM, and XGBoost models, we used a recursive feature elimination algorithm. This approach began with all features and iteratively removed the least important ones based on feature importance rankings.[118, 119] The elimination process continued until the highest area under the receiver operating characteristic curve (AUROC) was achieved. The final feature set at this point was selected as the optimal input for each model.

Evaluation of Prediction Performance

We evaluated model performance using classification accuracy, F1 score, and AUROC. These metrics were calculated using the test dataset to ensure an unbiased assessment of each model's predictive capability. Among them, AUROC served as the primary metric for selecting the best-performing model for forecasting the risk of endocrine-related irAEs.[120] AUROC evaluates a model's ability to distinguish between patients who will and will not experience endocrine-related irAEs across all classification thresholds.[120] It is robust to class potential imbalance sample size, making it a reliable metric for model performance evaluation.

We adjusted the decision threshold to align with the true event probability, rather than relying on the default threshold of 0.50.[120] To reduce potential sampling bias and ensure robustness, we repeated the entire process of data splitting, training, and testing 100 times.[121] We reported the average model performance and corresponding 95% confidence intervals (CI) across these iterations.

Evaluation of Feature Importance

In the LASSO logistic regression, the magnitude of the model coefficients reflects the relative importance of the corresponding features. In the tree-based models (RF and XGBoost), feature importance was assessed by the mean decrease in the Gini index, which reflects how much each feature contributed to reducing node impurity. A higher mean decrease indicated greater importance.[122] For SVM, feature importance was evaluated based on each feature's effect on AUROC. The best-performing model among the four candidates was selected as the final model for assessing feature importance. We computed Shapley Additive exPlanations (SHAP) values for the best-performing model to interpret how features contribute to predictions. Rooted in cooperative game theory, SHAP values quantify the contribution of each feature to the model's output.[156] All statistical analyses were performed using R version 4.2.3 in RStudio.

Results

Patient Sample Characteristics

A total of 4,222 patients with mNSCLC who initiated ICIs met the study's inclusion criteria. Among them, 892 (21.1%) developed endocrine irAEs within three months of starting ICI treatment. The most common endocrine irAEs were hypothyroidism (n=799; 89.6%), followed by type 1 diabetes (n=105; 11.8%), and hyperthyroidism (n=77; 8.6%). Less frequently observed events included adrenal insufficiency (5.4%), thyroiditis (2.2%), and, at rates below 1.3%, hypopituitarism, hypophysitis, and Cushing syndrome (**Table 1**).

Patients who had endocrine irAEs had a higher proportion of females compared to those with non-endocrine irAEs (57.4% vs. 44.5%; $p < 0.001$) and a slightly higher median age (76 vs. 75 years; p=0.038). Regional variation was also noted (p=0.006), with a higher proportion of cases in the Northeast (36.9% vs. 31.4%). In terms of treatment, a smaller proportion of patients

with endocrine irAEs received atezolizumab (1.3% vs. 2.6%; p<0.001) or chemotherapy (42.4% vs. 50.2%; p<0.001) than those without endocrine irAEs. Several baseline comorbidities were more prevalent in the endocrine irAEs group, including type 2 diabetes (30.4% vs. 23.4%; p<0.001) and renal disease (13.9% vs. 10.4%; p=0.004). Notably, participants with endocrine irAEs exhibited significantly higher rates of pre-existing endocrine conditions, such as hypothyroidism (42.8% vs. 9.2%; p<0.001), hyperthyroidism (2.2% vs. 0.7%; p<0.001), and type 1 diabetes (4.7% vs. 1.3%; p<0.001), than those without endocrine irAEs.

Regarding the socioeconomic factors, patients who developed endocrine irAEs had a slightly higher median Yost Index (10,706.5 vs. 10,599.5; p=0.002) and resided in census tracts characterized by a lower percentage of adults without a high school diploma (11.7% vs. 12.5%; p=0.018) and a higher median household income ($56,081 vs. $53,620; p=0.016), compared with those who did not develop endocrine irAEs.

Model Performance

Table 2 presents the performance of LASSO and the other three ML models in predicting 3-month endocrine irAEs among patients with mNSCLC receiving first-line ICI therapy. Overall, the LASSO model achieved the highest accuracy, F1 score, and AUROC, indicating greater performance in identifying patients who developed endocrine irAEs. Specifically, LASSO showed an accuracy of 0.791 (95% CI, 0.789–0.793), F1 score of 0.507 (95% CI, 0.502–0.512), and AUROC of 0.724 (95% CI, 0.719–0.728). Random Forest demonstrated comparable performance, with an accuracy of 0.787 (95% CI, 0.785–0.789); F1 score of 0.497 (95% CI, 0.492–0.503); AUROC of 0.711 (95% CI, 0.707–0.715). XGBoost and SVM models demonstrated lower performance across all evaluation metrics.

Among 4,222 patients, 1,162 (27.5%) developed endocrine irAEs within six months of ICI initiation. **Table 3** presents the results from sensitivity analysis 1, which were consistent with the main findings. LASSO again outperformed the other models, achieving the highest accuracy of 0.732 (95% CI, 0.730–0.735), F1 score of 0.514 (95% CI, 0.509–0.519), and AUROC of 0.701 (95% CI, 0.697–0.705). Random Forest ranked second, with an AUROC of 0.700 (95% CI, 0.696–0.703), F1 score of 0.513 (95% CI, 0.508–0.518), and AUROC of 0.700 (95% CI, 0.696–0.703). XGBoost and SVM continued to show lower AUROC than LASSO.

After excluding patients with pre-existing endocrine conditions, a total of 3,434 patients remained in the cohort. Among them, 467 (13.6%) developed new endocrine irAEs within three months of ICI therapy. **Supplementary Table 3** presents the results of sensitivity analysis 2. Among all models, LASSO demonstrated the best overall performance, with the highest accuracy of 0.777 (95% CI: 0.774–0.779), F1 score of 0.196 (95% CI: 0.189–0.203), and AUROC of 0.572 (95% CI: 0.566–0.577). Random Forest demonstrated modest performance, with an accuracy of 0.773 (95% CI: 0.772–0.775), F1 score of 0.176 (95% CI: 0.169–0.182), and AUROC of 0.540 (95% CI: 0.535–0.545). XGBoost and SVM continued to show comparatively lower discriminative ability, with AUROC values of 0.524 (95% CI: 0.520–0.529) and 0.517 (95% CI: 0.510–0.525), respectively.

Figure 3 and **Supplementary Figures 1-3** present feature importance plots for LASSO, XGBoost, Random Forest, and SVM models in predicting 3-month endocrine irAEs. While the specific ranking of predictors varies slightly across models, several features—such as pre-existing endocrine conditions, demographic factors (e.g., sex, age, race, region), socioeconomic conditions, and comorbidities—consistently appear among the top contributors. The LASSO model, which demonstrated the strongest predictive performance, was visualized using SHAP

values to illustrate the directional impact of key variables on endocrine irAEs. The analysis identified pre-existing endocrine conditions—including hypothyroidism, type 1 diabetes, hyperthyroidism, hypopituitarism, and type 2 diabetes—as significant predictors associated with an increased risk of endocrine irAEs (**Figure 4**). Conversely, patients receiving atezolizumab and ICI combined with chemotherapy exhibited a lower likelihood of experiencing endocrine irAEs. Additionally, male sex, residence in the western or southern U.S., and non-white race were also associated with a lower risk of endocrine irAEs.

The sensitivity analysis 1 results of the feature importance of the four models are presented in **Supplementary Figures 4–7**. The LASSO model's sensitivity analysis was consistent with the main findings regarding the importance and direction of pre-existing conditions and demographic factors. Notably, among the top 10 influencers, the model also identified pneumonitis and liver disease as significant predictors, both of which were negatively associated with the risk of endocrine irAEs incidence at six months (**Supplementary Figure 8**).

The results of feature importance from sensitivity analysis 2 are presented in **Supplementary Figures 9–12**. Key predictors of newly developed endocrine toxicity included specific ICI regimens, pre-existing type 2 diabetes, chemotherapy use, demographic characteristics, and cancer histology. Male sex, black race, residence in the southern U.S. and nonmetropolitan areas, absence of type 2 diabetes, nonsquamous histology, and treatment with atezolizumab and concurrent chemotherapy were associated with a lower likelihood of developing irAEs (**Supplementary Figure 13**).

Discussion

This study is among the first to demonstrate the feasibility of an ML approach with administrative claims-linked data to predict endocrine irAEs in mNSCLC patients initiating ICIs. Feature importance plots provided quantitative estimates of the contribution of individual features used in the predictive models. These features were organized into distinct domains, offering clinicians a clear visualization of the key factors that might impact the risk of endocrine irAEs among patients with mNSCLC receiving ICI therapy.

Our analysis found that the LASSO model outperformed RF, XGBoost, and SVM models in predicting endocrine irAEs among mNSCLC patients treated with first-line ICIs. Our findings are consistent with prior research that has identified risk factors for endocrine irAEs among patients receiving ICIs using other types of data sources and approaches. A systematic review of clinical trials reported that patients with pre-existing endocrine disorders are at higher risk for worsening of their underlying condition and the development of new endocrine irAEs.[157] More specifically, prior studies have shown that patients with pre-existing anti-thyroid antibodies are more likely to develop ICI-induced thyroid dysfunction.[158, 159] In our study, patients treated with PD-L1 inhibitor atezolizumab exhibited a lower risk of endocrine irAEs compared with those receiving PD-1 inhibitors, including pembrolizumab and nivolumab. This observation is consistent with findings from a network meta-analysis that reported no significant difference in the risk of hypothyroidism between PD-1 and PD-L1 inhibitors (adjusted P = .11), but a significantly higher risk of hyperthyroidism for PD-1compared to PD-L1 inhibitors (odds ratio = 5.36; 95% CI, 2.04-14.08, P = .002).[160]

Notably, we observed a marked decline in ML model performance when patients with pre-existing endocrine conditions were excluded from the analysis. This finding suggests that baseline endocrine comorbidities are likely the most influential predictors of the incidence of

endocrine irAEs following initiation of ICI therapy. We also found that patients who received concurrent chemotherapy had a lower risk of developing endocrine irAEs. This finding is consistent with prior research reported that patients treated with ICI combined with chemotherapy regimens experienced fewer irAEs compared to those receiving ICIs alone.[93] Our study also identified several strong demographic predictors of endocrine irAEs, including sex, race, and geographic region. In line with our findings, females were more likely to develop endocrine irAEs, largely driven by higher rates of thyroid toxicity, as reported in analyses of the FDA Adverse Event Reporting System database.[161, 162] However, there remains limited evidence regarding racial and regional disparities in the development of endocrine toxicity, warranting further investigation to better understand potential variation in outcomes.

To the best of our knowledge, no prior ML models have been developed to predict endocrine irAEs. One study focused specifically on ICI-induced hypothyroidism and demonstrated that the XGBoost algorithm achieved strong predictive performance, with an AUC of 0.833 using electronic health record data.[163] Consistent with our findings, the study identified that undiagnosed or subclinical pre-existing hypothyroidism was positively associated with the development of hypothyroidism after ICIs, while concurrent chemotherapy and male sex were associated with a lower likelihood. The superior performance of their model may be partly attributed to the inclusion of richer clinical variables that were not available in our dataset, including thyroid-stimulating hormone levels, body mass index, and smoking history.[163]

There are several limitations to this study. First, there is no widely accepted definition of endocrine irAEs within medical claims data. In this analysis, we employed a broad definition encompassing a range of endocrine conditions, which may have resulted in an overestimation of endocrine irAE outcomes.[115] However, as this definition was consistently applied across both the

training and testing cohorts, its impact on model performance is expected to be minimal. Secondly, the incidence of endocrine irAEs could be influenced by competing risks such as mortality, which were not accounted for in our analysis. In the sensitivity analysis 1, we identified that pre-existing pneumonitis and liver disease were negatively associated with the occurrence of endocrine irAEs. However, this finding should be interpreted with caution, as it may reflect higher early mortality among patients with these conditions, potentially preventing the development or detection of endocrine irAEs. Future studies employing advanced survival-based ML techniques, such as random survival forests, may consider the endocrine irAEs as time-to-event outcomes and death as competing risks.[164] Additionally, SEER-Medicare does not capture certain important clinical features related to endocrine irAEs, such as PD-L1 expression, thyroid-stimulating hormone levels, and free thyroxine levels. The lack of clinically relevant features limited our model's predictive performance. Furthermore, the SEER-Medicare database may be affected by missing data, coding inaccuracies, and misclassification, which could introduce measurement bias. Lastly, because our study population was restricted to Medicare beneficiaries, the findings may not be generalizable to younger individuals or those covered by other insurance plans.

In conclusion, using a cancer registry linked with Medicare claims data, the LASSO model demonstrated the strongest predictive performance for endocrine irAEs in patients with mNSCLC receiving ICIs compared to ML approaches, including Random Forest, XGBoost, and SVM. Baseline endocrine conditions were identified as the most influential predictors of endocrine toxicity after ICI therapy. In addition, demographic characteristics, the specific ICI agent administered, and concurrent chemotherapy utilization also played significant roles in predicting the risk of endocrine irAEs. The consistent identification of key risk factors across

models provides valuable insights for clinical risk stratification and supports proactive strategies for patients at increased risk of developing these AEs. Future research is warranted to improve prediction performance by incorporating additional clinically relevant features and applying time-to-event ML models to provide a more comprehensive understanding of ICI-associated endocrine toxicity.

Figure 1. Overview of predictive model development

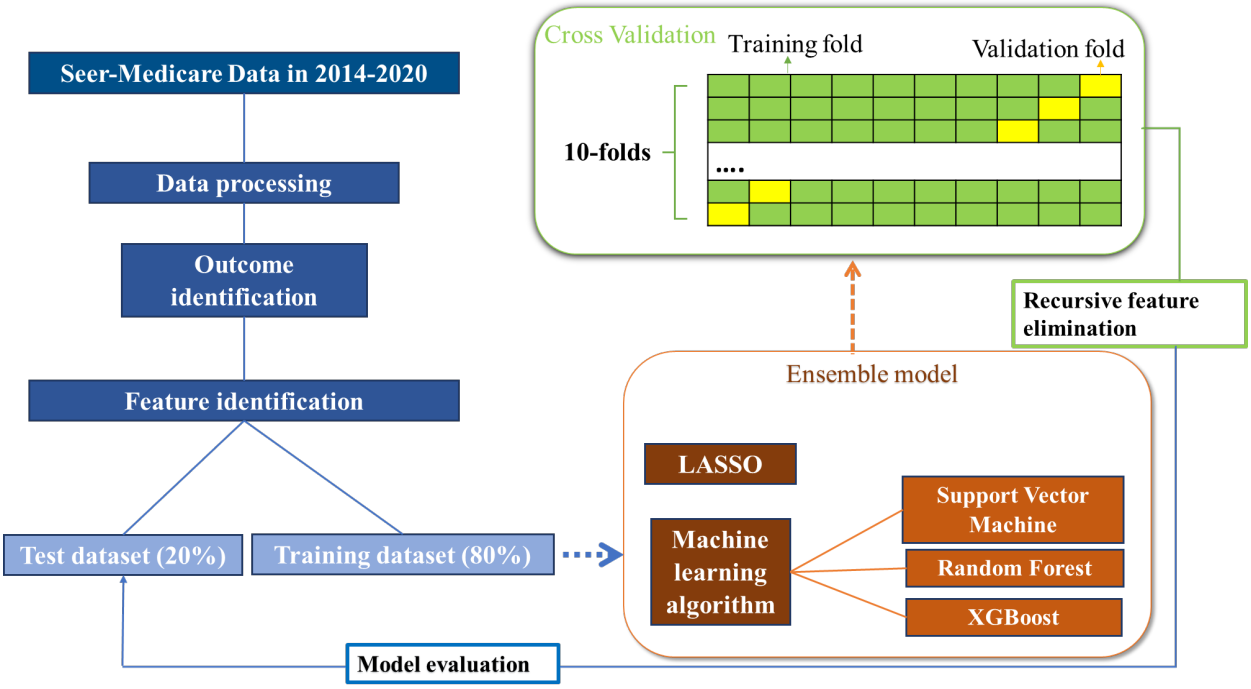


Figure 2. Flowchart of patient inclusion and exclusion

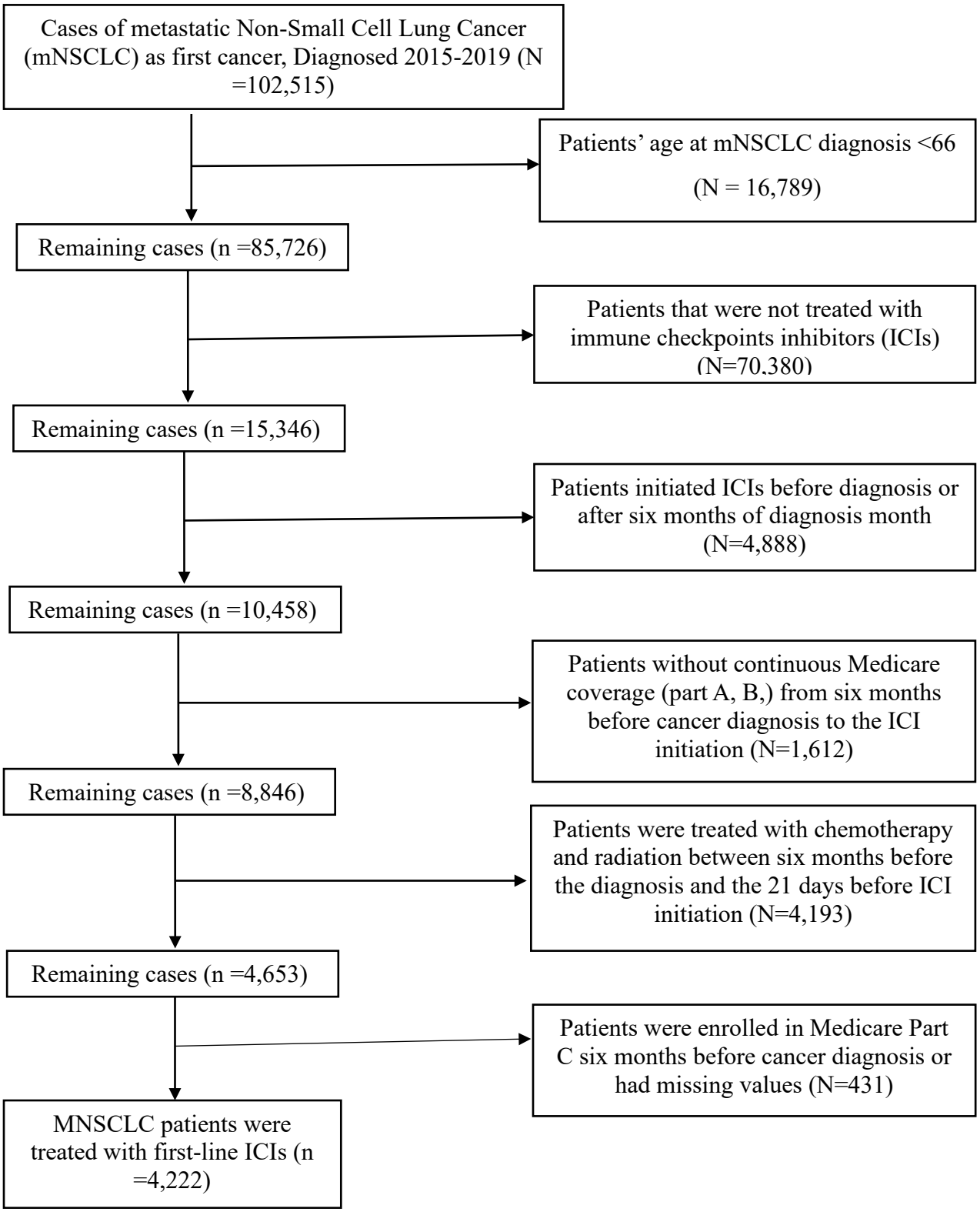


Figure 3. Feature importance for LASSO in predicting the 3-month risk of endocrine-related irAEs

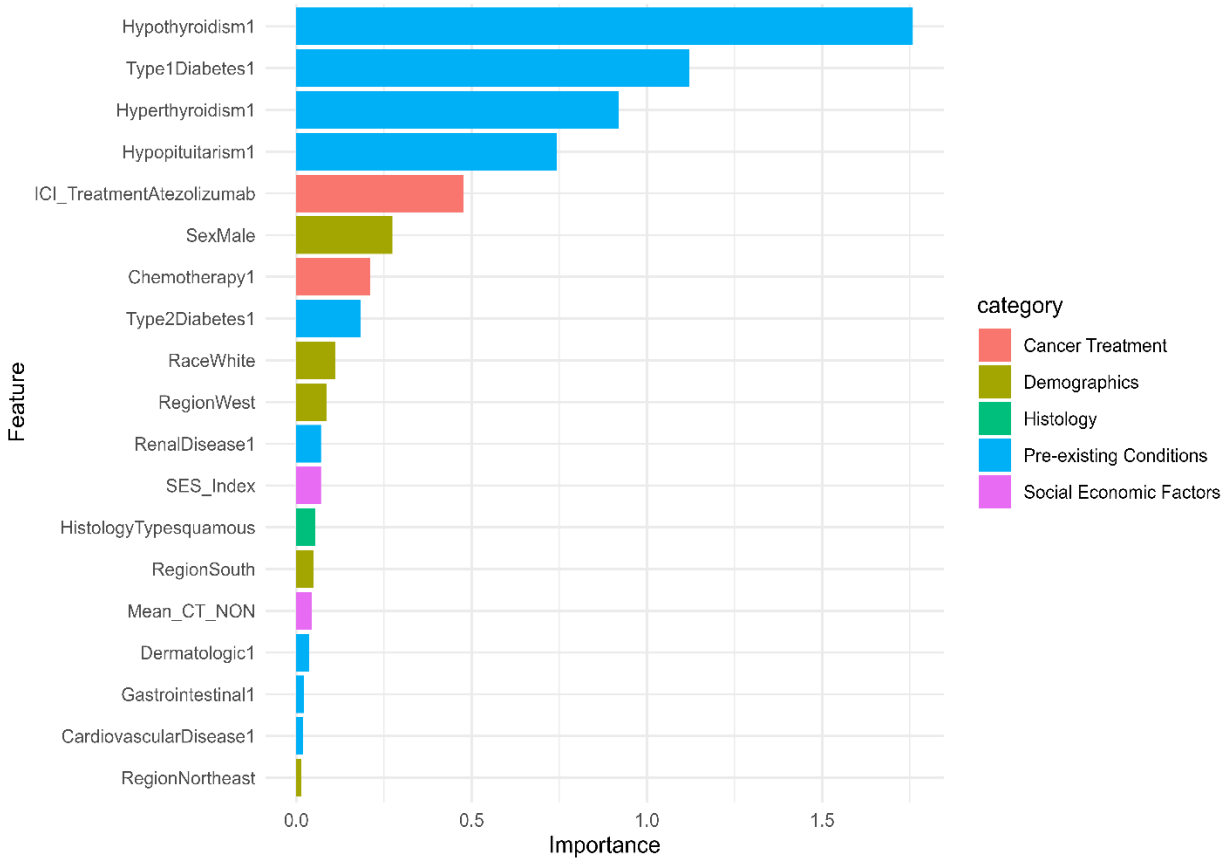


Figure 4. SHAP value for LASSO in predicting the 3-month risk of endocrine-related irAEs

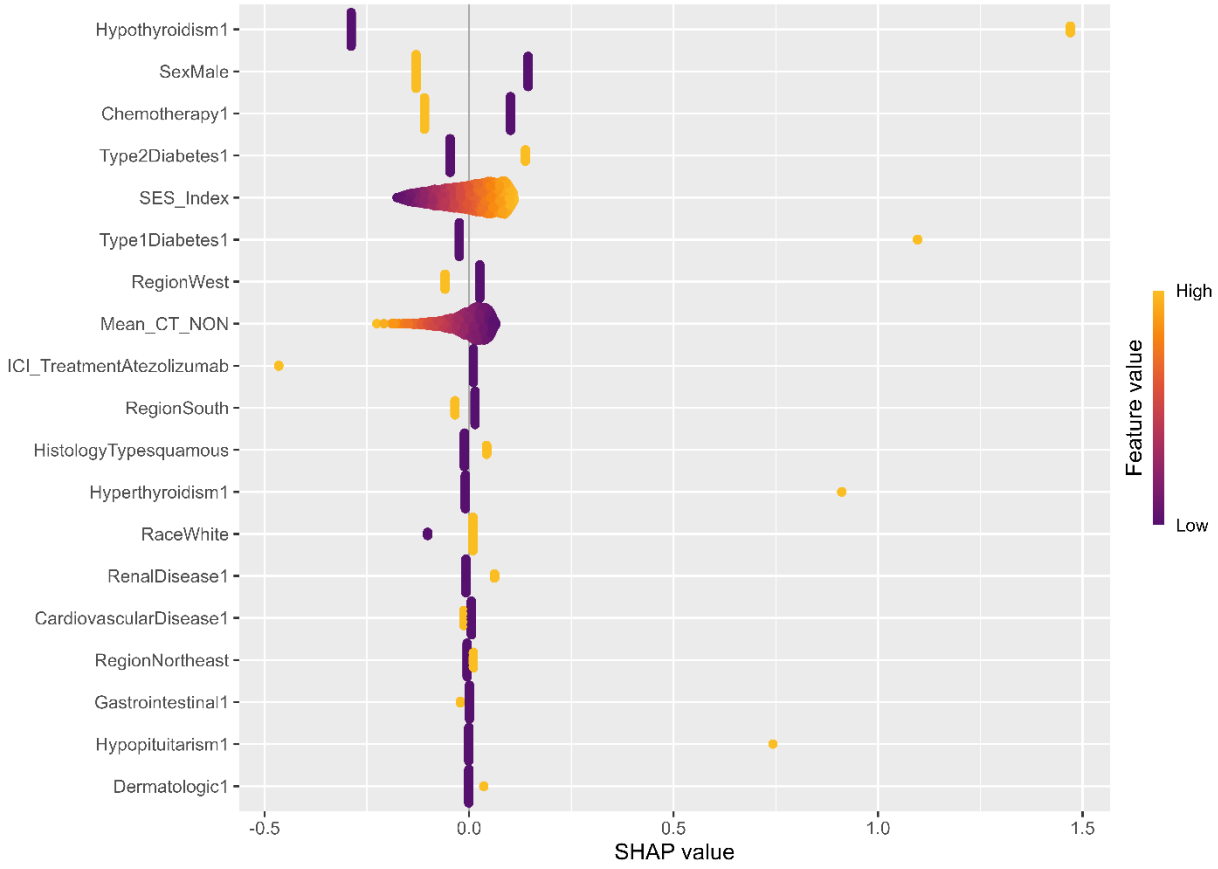


Table 1. Patient characteristics

Characteristic	Non-endocrine-related irAEs N = 3,330[1]	Endocrine-related irAEs N = 892[1]	p-value[2]
Age	75.0 (66.0, 90.0)	76.0 (66.0, 90.0)	0.038
Residence			0.13
Metropolitan	2,815 (84.5%)	773 (86.7%)	
Nonmetropolitan	515 (15.5%)	119 (13.3%)	
Sex			<0.001
Female	1,483 (44.5%)	512 (57.4%)	
Male	1,847 (55.5%)	380 (42.6%)	
Race/Ethnicity			0.087
Asian	47 (1.4%)	12 (1.3%)	
Black	161 (4.8%)	27 (3.0%)	
Other/Hispanic/Native	82 (2.5%)	17 (1.9%)	
White	3,040 (91.3%)	836 (93.7%)	
Histology			0.8
nonsquamous	2,642 (79.3%)	703 (78.8%)	
squamous	688 (20.7%)	189 (21.2%)	
Region			0.006
Midwest	251 (7.5%)	77 (8.6%)	
Northeast	1,047 (31.4%)	329 (36.9%)	
South	1,016 (30.5%)	247 (27.7%)	
West	1,016 (30.5%)	239 (26.8%)	
Time To ICI Initiation	55.0 (21.0, 138.0)	55.0 (20.0, 140.0)	0.7
ICI_Treatment			0.039
Atezolizumab	87 (2.6%)	12 (1.3%)	

Nivolumab	168 (5.0%)	55 (6.2%)	
Pembrolizumab	3,075 (92.3%)	825 (92.5%)	
Chemotherapy			<0.001
No	1,658 (49.8%)	514 (57.6%)	
Yes	1,672 (50.2%)	378 (42.4%)	
Radiotherapy			0.7
No	2,615 (78.5%)	707 (79.3%)	
Yes	715 (21.5%)	185 (20.7%)	
Adjusted Charlson Comorbidity	1.0 (0.0, 5.0)	1.0 (0.0, 5.0)	<0.001
Dermatologic			0.4
No	3,283 (98.6%)	875 (98.1%)	
Yes	47 (1.4%)	17 (1.9%)	
Hematologic			0.6
No	3,278 (98.4%)	875 (98.1%)	
Yes	52 (1.6%)	17 (1.9%)	
Pneumonitis			0.2
No	2,909 (87.4%)	765 (85.8%)	
Yes	421 (12.6%)	127 (14.2%)	
Type2Diabetes			<0.001
No	2,550 (76.6%)	621 (69.6%)	
Yes	780 (23.4%)	271 (30.4%)	
Gastrointestinal			0.8
No	3,193 (95.9%)	858 (96.2%)	
Yes	137 (4.1%)	34 (3.8%)	
Renal Disease			0.004

No	2,983 (89.6%)	768 (86.1%)	
Yes	347 (10.4%)	124 (13.9%)	
Cardiovascular Disease			0.2
No	2,306 (69.2%)	598 (67.0%)	
Yes	1,024 (30.8%)	294 (33.0%)	
Liver Disease			0.7
No	3,250 (97.6%)	868 (97.3%)	
Yes	80 (2.4%)	24 (2.7%)	
Musculoskeletal Disease			0.064
No	3,148 (94.5%)	828 (92.8%)	
Yes	182 (5.5%)	64 (7.2%)	
COPD			0.7
No	2,336 (70.2%)	632 (70.9%)	
Yes	994 (29.8%)	260 (29.1%)	
Hypothyroidism			<0.001
No	3,025 (90.8%)	510 (57.2%)	
Yes	305 (9.2%)	382 (42.8%)	
Hyperthyroidism			<0.001
No	3,308 (99.3%)	872 (97.8%)	
Yes	22 (0.7%)	20 (2.2%)	
Type 1 Diabetes			<0.001
No	3,287 (98.7%)	850 (95.3%)	
Yes	43 (1.3%)	42 (4.7%)	
Cushing Syndrome*			0.9
No	3,327 (>99.79%)	>881 (>98.7%)	
Yes	<11 (<0.3%)	<11 (<1.3%)	

Hypopituitarism*			0.2
No	3,327 (>99.79%)	>881 (>98.7%)	
Yes	<11 (<0.3%)	<11 (<1.3%)	
Thyroiditis*			>0.9
No	3,327 (>99.79%)	>881 (>98.7%)	
Yes	<11 (<0.3%)	<11 (<1.3%)	
Yost_Index	10,599.5 (8,649.0, 11,753.3)	10,706.5 (8,675.5, 11,755.7)	0.002
CT_NON[3]	12.5 (1.8, 39.3)	11.7 (2.2, 36.7)	0.012
Household Median Income	53,619.7 (24,438.1, 121,497.1)	56,080.7 (26,036.3, 116,721.5)	0.016
Endocrine-related AEs			
Hypothyroidism	NA	799 (89.6%)	
Hyperthyroidism		77 (8.6%)	
Type1Diabetes		105 (11.8%)	
Hypophysitis*		<11 (<1.3%)	
Adrenal Insufficiency		48 (5.4%)	
Cushing Syndrome*		<11 (<1.3%)	
Hypopituitarism*		<11 (<1.3%)	
Thyroiditis		20 (2.2%)	

[1]No. (%) for categorical variables; median (2.5th–97.5th percentile) for continuous variables
[2]Pearson's Chi-squared test; Welch Two Sample t-test
[3]% of households with an education level below high school(Census Tract)
*: suppressed due to cell size < 11

Table 2. Prediction performance for each machine learning model in predicting the 3-month risk of endocrine-related irAEs

Model	Accuracy (95% CI)	F1 Score (95% CI)	AUROC (95% CI)
Random Forest	0.7870 [0.7846, 0.7894]	0.4973 [0.4917, 0.5030]	0.7112 [0.7071, 0.7153]
XGBoost	0.7194 [0.7171, 0.7216]	0.4138 [0.4091, 0.4184]	0.6655 [0.6616, 0.6694]
SVM	0.7696 [0.7672, 0.7719]	0.4552 [0.4497, 0.4608]	0.6629 [0.6585, 0.6672]
LASSO	0.7914 [0.7894, 0.7934]	0.5068 [0.5020, 0.5116]	0.7236 [0.7194, 0.7277]

AUROC = Area Under the Receiver Operating Characteristic Curve; CI = Confidence Interval

Table 3. Prediction performance for each machine learning model in predicting the 6-month risk of endocrine-related irAEs

Model	Accuracy (95% CI)	F1 Score (95% CI)	AUROC (95% CI)
Random Forest	0.7626 [0.7601, 0.7651]	0.5130 [0.5079, 0.5181]	0.6996 [0.6960, 0.7032]
XGBoost	0.7002 [0.6979, 0.7025]	0.4558 [0.4517, 0.4599]	0.6535 [0.6500, 0.6570]
SVM	0.7134 [0.7109, 0.7159]	0.4799 [0.4754, 0.4844]	0.6645 [0.6607, 0.6682]
LASSO	0.7323 [0.7295, 0.7352]	0.5142 [0.5090, 0.5193]	0.7009 [0.6970, 0.7049]

AUROC = Area Under the Receiver Operating Characteristic Curve; CI = Confidence Interval

Aim 3 Manuscript

As noted in the limitations of Chapter 3, 14.8% of patients in the EMPOWER-Lung 3 trial had unresectable locally advanced NSCLC. To ensure consistency in population definition for evaluating the cost-effectiveness of the new CCT regimen, the following manuscript will focus on patients with advanced NSCLC, including both locally advanced and metastatic disease.

Title: Cost-effectiveness of cemiplimab plus chemotherapy vs pembrolizumab plus chemotherapy as first-line treatment for advanced non-small cell lung cancer

Abstract

Background: In 2022, the US Food and Drug Administration approved cemiplimab in combination with chemotherapy (CCT) as a first-line treatment for advanced non–small cell lung cancer (aNSCLC). However, whether CCT presents a cost-effective alternative to the previously preferred first-line treatment, pembrolizumab plus chemotherapy (PCT), remains uncertain.

Objective: To evaluate the cost-effectiveness of CCT vs PCT as the first-line treatment for aNSCLC from a US health care payer perspective.

Methods: A 3-state partitioned survival model with a 10-year horizon was constructed. Clinical data were derived from the EMPOWER-Lung 3, KEYNOTE-407, and KEYNOTE-189 trials. Costs and quality of life were obtained from published 2024 US list prices and literature. The cost, quality-adjusted life-years (QALYs) gained, and incremental cost-effectiveness ratio (ICER) were calculated. All outcomes were discounted at a rate of 3% per year. Scenario analyses, deterministic and probabilistic sensitivity analyses, and subgroup analyses were performed for patients with different programmed death ligand 1 (PD-L1) levels.

Results: In the base-case analysis, the total cost of PCT was $207,926 with 1.609 QALYs, whereas CCT had a total cost of $175,247 with 1.657 QALYs. Results from the scenario analyses were consistent with the base-case analysis, indicating that CCT was a dominant treatment strategy over PCT (ICER=−$675,304 per QALY). The cost of pembrolizumab highly impacted the ICER. At a willingness-to-pay threshold of $150,000 per QALY, CCT would be accepted as a cost-effective option 96.9% of the time. In subgroup analyses, CCT remained a dominant alternative to PCT for patients with PD-L1 levels of at least 50% and 1%-49%.

Conclusions: This cost-effectiveness analysis suggests that CCT is a dominant first-line treatment option for aNSCLC with PD-L1 levels of at least 1% compared with PCT.

1. Introduction

Lung cancer is the second most prevalent cancer and first leading cause of cancer death in the United States (U.S.).[1] In 2023, there were 238,340 new cases of lung cancer and 127,070 lung cancer-related fatalities in the U.S., accounting for 12.2% of total cancer incidence and 20.8% of cancer deaths.[1, 2] The main types of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) based on histology, with NSCLC accounting for 80-85% of cases.[3] Approximately 70% of lung cancer patients are diagnosed at advanced or metastatic stages, where the five-year relative survival rate is less than 9% for advanced NSCLC (aNSCLC).[137]

Immunotherapy has significantly improved the survival outcomes of patients with aNSCLC. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that block specific proteins in immune cells and cancer cells, enhancing the immune system to recognize and attack cancer cells more effectively.[5] However, immunotherapy is expensive. In 2021, the average drug cost (total cost paid by payers and patients) for patients undergoing immunotherapy was $132,582 per year, significantly surpassing the average drug cost of $26,095 per year for cancer patients not receiving immunotherapy in the U.S.[165] Although only 12.1% of cancer patients received immunotherapy in 2021, it accounted for 36.2% of total oncology medication spending in the U.S.[165] The high cost of ICIs puts a substantial financial burden on both patients and the healthcare system, leading to delayed care and reduced quality of life.[14, 15] Assessing the cost-effectiveness of ICIs is crucial for informing treatment decisions for patients and the healthcare system.

According to the National Comprehensive Cancer Network (NCCN) guidelines, pembrolizumab, as programmed cell death protein 1 (PD-1) receptor inhibitor, combined with chemotherapy (PCT), is the preferred first-line treatment for patients with aNSCLC regardless of programmed cell death ligand 1 (PD-L1) levels.[166] In the five-year follow-up results of Phase 3 KEYNOTE-407 trial, PCT significantly improved overall survival (OS) compared to chemotherapy alone in patients with squamous aNSCLC (hazard ratio (HR) = 0.71, 95% confidence interval (CI): 0.59-0.85) and also enhanced progression-free survival (PFS) (HR = 0.62, 95% CI: 0.52-0.74).[38] Similarly, the Phase 3 KEYNOTE-189 trial demonstrated that first-line PCT significantly improved OS (HR = 0.60, 95% CI: 0.50-0.72) and PFS (HR = 0.50, 95% CI: 0.42-0.60) in patients with non-squamous aNSCLC.[23] PCT has also been considered the preferred cost-effective regimen for aNSCLC patients without considering PD-L1 expression from the U.S. healthcare payer perspective compared to chemotherapy alone.[78] On November 8, 2022, the U.S. Food and Drug Administration (FDA) approved cemiplimab, a new generation PD-1 inhibitor, combined with chemotherapy (CCT) as a first-line treatment for patients with aNSCLC regardless of PD-L1 levels.[167] In the Phase 3 EMPOWER-Lung 3 trial, cemiplimab plus chemotherapy demonstrated superior OS and PFS over chemotherapy alone as a first-line treatment for aNSCLC (HR for OS = 0.65, 95% CI: 0.51-0.82; HR for PFS = 0.55, 95% CI: 0.44-0.68).[41] In addition, a prior cost-effectiveness analyses have found cemiplimab monotherapy to be a cost-effective first-line option for aNSCLC patients with PD-L1 ≥50% compared to pembrolizumab monotherapy from a U.S. payer perspective.[79] However, whether CCT presents a cost-effective alternative to PCT remains unknown and warrants further investigation. The objective of this study was to evaluate the cost-effectiveness of CCT compared with PCT from the US Medicare & Medicaid perspective.

2. Methods

This economic evaluation followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guidelines.[168] From the US Medicare & Medicaid payer perspective, we constructed a partitioned survival model (PSM) to simulate costs, quality of life, toxic effects, disease progression, and survival for aNSCLC patients treated with either first-line CCT or PCT (**Figure 1**). In the PSM, patients initially entered a progression-free state, then transitioned to progressive disease (PD), and ultimately to death, or they could directly progress to death from the progression-free state. We used a monthly cycle and a 10-year overall time horizon. Life-years and costs were discounted at an annual rate of 3%.[81, 131] The R package "heemod" was used to construct and analyze the PSM model and visualize the results.

2.1 Treatment details

We evaluated the treatment cost and effectiveness based on the updated follow-up outcomes from EMPOWER-Lung 3, KEYNOTE-407, and KEYNOTE-189 clinical trials.[23, 38, 41] EMPOWER-Lung 3 is a double-blind, placebo-controlled phase 3 study investigating the safety and efficacy of CCT versus chemotherapy alone as the first-line treatment for patients with aNSCLC.[41] KEYNOTE-407 and KEYNOTE-189 are double-blind, placebo-controlled phase 3 studies investigating PCT versus chemotherapy alone as the first-line treatment for aNSCLC patients with squamous and nonsquamous histology, respectively.[23, 38] In the EMPOWER-Lung 3 trial, patients received cemiplimab 350 mg every three weeks (one cycle) for up to 36 cycles along with four cycles of platinum-doublet chemotherapy (clinician’s choice of paclitaxel plus carboplatin, paclitaxel plus cisplatin, pemetrexed plus carboplatin, or pemetrexed plus cisplatin).[41] Nonsquamous patients received maintenance pemetrexed 500 mg per square meter

every three weeks. In the KEYNOTE-407 trial, squamous patients received 200 mg pembrolizumab every three weeks for up to 35 cycles, along with four cycles of platinum-doublet chemotherapy (paclitaxel or nanoparticle albumin-bound [nab]–paclitaxel plus carboplatin).[38] In the KEYNOTE-189 trial, nonsquamous patients received 200 mg pembrolizumab every three weeks for up to 35 cycles, along with four cycles of platinum-doublet chemotherapy (cisplatin or carboplatin plus pemetrexed).[23] After four cycles of platinum-doublet chemotherapy, patients were treated with pemetrexed every three weeks.[23]

2.2 Survival modeling

The OS and PFS probabilities for patients treated with first-line CCT and PCT were derived from the EMPOWER-Lung 3, KEYNOTE-407, and KEYNOTE-189 trials. [23, 38, 41] Kaplan-Meier (KM) survival curves were extracted using WebPlotDigitizer to capture the time-dependent probabilities of patients in progression-free states and PD states.[125] Subsequently, individual patient data (IPD) were simulated based on KM curves and fitted into standard parametric models, including exponential, Weibull, log-logistic, and log-normal distributions. The values of the Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used as metrics for the goodness of fit across the different parametric distributions (**Supplementary Table 1**). The models with the lowest AIC and BIC values were selected as the final survival distributions (**Supplementary Figure 1**).

Patients with different histological subtypes of aNSCLC exhibited varying levels of treatment efficacy with PCT and CCT.[23, 38, 41] In the EMPOWER-Lung 3 trial for CCT, 42.9% of

patients with aNSCLC exhibited squamous histology, while 57.1% had non-squamous histology.[41] To maintain consistency in the patient histology profile, the final OS and PFS models for PCT combined survival probabilities of squamous patients from KEYNOTE-407 and nonsquamous patients from KEYNOTE-189, with proportions of 42.9% and 57.1%, respectively.

2.3 Costs and utilities

This study included direct medical costs of therapeutic drugs, intravenous injection administration, follow-up care, and severe adverse events (SAEs) management (**Table 1**). [40-44]

Unit drug costs were derived from the Centers for Medicare & Medicaid Services (CMS) April 2024 Average Sales Price (ASP) drug pricing files.[39] Since the types of chemotherapy regimens differed among the KEYNOTE-407, KEYNOTE-189, and EMPOWER-Lung 3 trials, the costs of chemotherapy were calculated individually for each trial instead of using a uniform cost. The costs of administration for intravenous injection were derived from the CMS Physician Fee Schedule.[126] EMPOWER-Lung 3 did not report second-line treatment after CCT. KEYNOTE-407 and KEYNOTE-189 reported varied second-line treatment strategies based on clinicians' choices. Based on the literature review and expert opinions, we adopted the cost of best-supportive care after aNSCLC progression as the cost of second-line treatment for both groups.[44, 127, 128] We captured the treatment costs of SAEs, defined as grade ≥ 3 adverse events with more than 5% incidence in the clinical trials (**Supplementary Table 2**). The cost of best-supportive care and management costs associated with SAEs were derived from the literature.[127, 129, 130] The weighted average cost of treating SAEs was calculated and inputted into the PSM model.[130] All costs were adjusted to 2024 U.S. dollars using the U.S. Consumer Price Index.[131, 132]

The effectiveness of treatment was measured using QALYs. Health utility was measured on a scale from 0 to 1, where 1 represents optimal health, and 0 represents death. The baseline values for health utilities in the progression-free states and PD states were sourced from the published literature.[131, 133] SAEs resulted in a decrement in their health utility, also known as disutility. Same as OS and PFS, the weighted averages of cost and disutility for PCT with squamous and non-squamous lung cancer were calculated from KEYNOTE-407 and KEYNOTE-189, using proportions of 42.9% and 57.1%, respectively.[131, 133] For dosing calculations, we assumed that the patient weighs 70 kg, has a body surface area of 1.86 m^2, and a creatinine clearance of 70 mL/min, according to previous cost-effectiveness analyses of immunotherapies for patients with aNSCLC. [80, 134]

2.4 Base-case, sensitivity, and subgroup analyses

In the base-case analysis (**Table 2**), we calculated the total costs and quality-adjusted life years (QALYs) gained for patients with aNSCLC treated with first-line CCT and PCT. The incremental cost and incremental QALYs between CCT and PCT were then used to calculate the incremental cost-effectiveness ratio (ICER).

$$ICER = \frac{COST_{cemiplimab\ plus\ chemotherapy} - COST_{pembrolizumab\ plus\ chemotherapy}}{QALY_{cemiplimab\ plus\ chemotherapy} - QALY_{pembrolizumab\ plus\ chemotherapy}}$$

There were two main concerns in the base-case analysis. First, the disutility of SAEs for PCT was higher due to longer follow-up times. According to up-to-date published results, patients under treatment of CCT were followed for three years in the EMPOWER-Lung 3 trial, while

those with PCT were followed for five years in the KEYNOTE-407 and KEYNOTE-189 trials. Secondly, the survival probability in the primary analysis was solely based on clinical trials. We, therefore, performed two scenario analyses. In scenario analysis 1, the incidence of SAEs for PCT was derived from the same follow-up time as CCT in the midterm reports of the KEYNOTE-407 and KEYNOTE-189 trials. Scenario analysis 2 extrapolated the OS curve after 60 months using aNSCLC relative survival rates from the 2000-2020 U.S. Surveillance, Epidemiology, and End Results (SEER) data.[135] The survival rate from SEER was fitted to a Weibull distribution (**Supplementary Figure 2**).

We also conducted a one-way deterministic sensitivity analysis (DSA) of costs, health utilities, and SAEs-related disutility to identify variables that significantly impacted the uncertainty of the ICER. To further assess model uncertainty, we performed a probabilistic sensitivity analysis (PSA) using a Monte Carlo simulation with 10,000 iterations. Cost-related variables were modeled using gamma distributions, while utility-related variables were modeled using beta distributions in the PSA.

Patients with aNSCLC exhibited different treatment efficacy with PCT and CCT across different PD-L1 expression levels. [23, 38, 41] For the subgroup analyses, we compared the cost-effectiveness of CCT versus PCT as the first-line treatment for patients with aNSCLC at different PD-L1 levels: ≥50%, 1%-49%, and <1%. The EMPOWER-Lung 3, KEYNOTE-407, and KEYNOTE-189 trials reported the HRs of OS and PFS for CCT and PCT compared to chemotherapy alone at different PD-L1 levels.[23, 38, 41] To derive the HR between CCT and PCT at different PD-L1 levels, we conducted a fixed-effect network meta-analysis (NMA) using the "netmeta" package in R.[136] First, we extracted the HRs for OS and PFS, along with their 95% confidence intervals, for CCT and PCT compared to chemotherapy alone from the EMPOWER-

Lung 3, KEYNOTE-407, and KEYNOTE-189 trials. [23, 38, 41] Next, we employed a fixed-effect model in the network meta-analysis to calculate the HRs between CCT and PCT at different PD-L1 levels (**Supplementary Table 3**). The OS and PFS for PCT were calculated by raising the OS and PFS of CCT to the power of the HRs between PCT and CCT.

$$OS_{PCT} = {OS_{CCT}}^{HR_{OS}}$$

$$PFS_{PCT} = {PFS_{CCT}}^{HR_{PFS}}$$

3. Results

3.1 Base-case analysis

In the base-case analysis, the total cost of PCT was $207,926, with a total of 1.609 QALYs gained. CCT had a total cost of $175,247 with 1.657 QALYs gained. The incremental cost of CCT compared to PCT was -$32,679, and the incremental QALYs gained were 0.048. This resulted in an ICER of -$675,304 per QALY with CCT (**Table 2**).

3.2 Sensitivity analyses

In scenario analysis 1, the total cost of PCT was $207,768, yielding a total of 1.612 QALYs gained. For CCT, the total cost remained $175,247 with 1.657 QALYs gained. The incremental cost difference between CCT and PCT was -$32,522, with an incremental gain of 0.044 QALYs. The corresponding ICER was -$731,180 per QALY with CCT.

Scenario analysis 2 showed that the total cost of PCT was $206,876 with 1.594 QALYs gained. CCT had a total cost of $175,247 and 1.655 QALYs gained. The incremental cost of CCT compared to PCT was -$31,799, and the incremental QALYs were 0.060. The ICER for this scenario was -$528,262 per QALY with CCT. The base-case and scenario analyses consistently suggested that CCT is a dominant strategy over PCT, as it is more effective and costs less.

The DSA evaluated the robustness of the cost-effectiveness results by varying key parameters. When evaluating costs, the DSA showed that the cost difference was most sensitive to the cost of pembrolizumab. The DSA of effectiveness showed the effectiveness difference was most sensitive to the SAE disutility associated with PCT (**Supplementary Figure 3**). The DSA of ICER indicated that the costs of pembrolizumab exerted the greatest impact on the ICER. In addition, the cost of cemiplimab, the SAE disutility associated with PCT, and the health utility in the PFS state significantly influenced ICER. (**Figure 2**) The PSA showed that CCT had a 93.3% probability of being a dominant choice over PCT, as it incurred lower costs and achieved higher QALYs (**Figure 3**). At a willingness-to-pay (WTP) threshold of $150,000 USD per QALY gained, CCT would be a cost-effective option 96.9% of the time. As the WTP increased from $0 to $300,000, the acceptability of CCT as a cost-effective option rose to 98.5% (**Supplementary Figure 4**).

3.3 Subgroup analyses

Our subgroup analyses compared the cost-effectiveness of CCT versus PCT across different PD-L1 expression levels (**Supplementary Table 4**). The assumed CCT cost of $175,247 and 1.657 QALYs gained remained the same across all subgroups. For patients with PD-L1 expression ≥50%, PCT had a total cost of $210,163 and 1.537 QALYs gained. The incremental cost of CCT

compared to PCT was -$34,916, with an incremental gain of 0.119 QALYs, resulting in an ICER of -$291,569 per QALY with CCT. In the subgroup of patients with 1%-49%, PCT had a total cost of $188,617 and 1.194 QALYs gained. The incremental cost of CCT was -$13,370, with an incremental gain of 0.463 QALYs, resulting in an ICER of -$28,900 per QALY with CCT. For patients with PD-L1 < 1%, PCT was associated with a total cost of $228,774 and 1.749 QALYs gained. The incremental cost of CCT was -$52,527, but with a slight decrement in QALYs of 0.092, resulting in an ICER of $578,974 per QALY with CCT.

4. Discussion

Our findings demonstrated that CCT, as a first-line treatment for patients with aNSCLC, results in lower cost and higher QALYs than PCT from the US Medicare & Medicaid payer perspective. The ICER results were mainly driven by the lower cost of cemiplimab compared to pembrolizumab and the superior safety profile of CCT compared to PCT.

In the base-case analysis, the ICER of -$675,304 per QALY with CCT showed that CCT is a dominant strategy over PCT, as it is more effective and less costly. The results were consistent across two different scenario analyses. The tremendous ICER value was led by the significant cost difference (-$32,679) in the numerator and the slight QALY difference (0.048) in the denominator. The base-case and scenario analyses consistently indicated that the cost differences were not lower than $30,000, and the effectiveness differences were not higher than 0.1 QALYs.

The primary driver for the slightly increased QALYs with CCT was its superior safety profile compared to PCT. EMPOWER-Lung 3 reported that patients receiving CCT experienced fewer SAEs than those receiving PCT in the KEYNOTE-407 and KEYNOTE-189 trials.[23, 38, 41]

The rate of grade ≥ 3 AEs was 48.7% for patients treated with CCT in the EMPOWER-Lung 3 trial, whereas the rates were 74.8% and 72.8% for patients treated with PCT in the KEYNOTE-407 and KEYNOTE-189 trials, respectively.[23, 38, 41] The reduction in SAE rates translated into better quality of life for patients who received CCT than those with PCT. The uncertainty of SAE rates, caused by different follow-up times in the EMPOWER-Lung 3, KEYNOTE-407, and KEYNOTE-189 trials, were examined in scenario analysis 1 to assess SAE rates treated with PCT from the mid-term follow-up reports in KEYNOTE-407 and KEYNOTE-189 trials.[169, 170]

The subgroup analyses were based on the HRs of OS and PFS of CCT versus PCT across different PD-L1 expression levels. For patients with PD-L1 ≥50% and 1%-49%, CCT remained a dominant alternative to PCT. For patients with PD-L1 < 1%, PCT was more expensive and effective than CCT, resulting in a positive ICER of $578,974 for CCT. The NMA indicated that for patients with PD-L1 < 1%, those treated with PCT showed better OS and PFS in the KEYNOTE-407 and KEYNOTE-189 trials compared to those treated with CCT in the EMPOWER-Lung 3 trial.[23, 38, 41] Given that the EMPOWER-Lung 3 trial did not report the OS and PFS curves for patients treated with CCT at different PD-L1 expression levels, further evaluation is warranted to examine subgroup analysis results when more data becomes available.

Three published studies compared the cost-effectiveness of CCT as the first-line treatment for patients with aNSCLC to chemotherapy alone from a U.S. healthcare payer perspective.[84, 171, 172] One study demonstrated that CCT is a cost-effective choice based on a WTP threshold of $150,000 per QALY.[172] The other two studies concluded that CCT is unlikely to be cost-effective compared to chemotherapy alone at the same threshold.[84, 171] The main difference is that the first study used the updated 2-year follow-up results of EMPOWER-Lung 3, whereas the other two studies used the original clinical reports with shorter follow-up times. [84, 171, 172] In the original

reports, the HR of OS was 0.71 (0.53-0.93) for CCT compared to chemotherapy alone, whereas in the 2-year follow-up results, the HR for OS improved to 0.65 (0.51-0.82).[41, 172] In other words, CCT is a cost-effective first-line treatment for patients with aNSCLC compared to chemotherapy alone from the perspective of the U.S. healthcare payer, using the latest clinical trial evidence.[173] Another study showed that cemiplimab monotherapy is a cost-effective first-line treatment for patients with aNSCLC with PD-L1 ≥50% compared to pembrolizumab monotherapy.[79] Specifically, cemiplimab monotherapy generated 1.00 incremental QALYs with an ICER of $68,254 per QALY compared to pembrolizumab monotherapy, which was below the WTP of $100,000.[79] These results aligned with our findings and further supported the economic value of cemiplimab-based regimens.

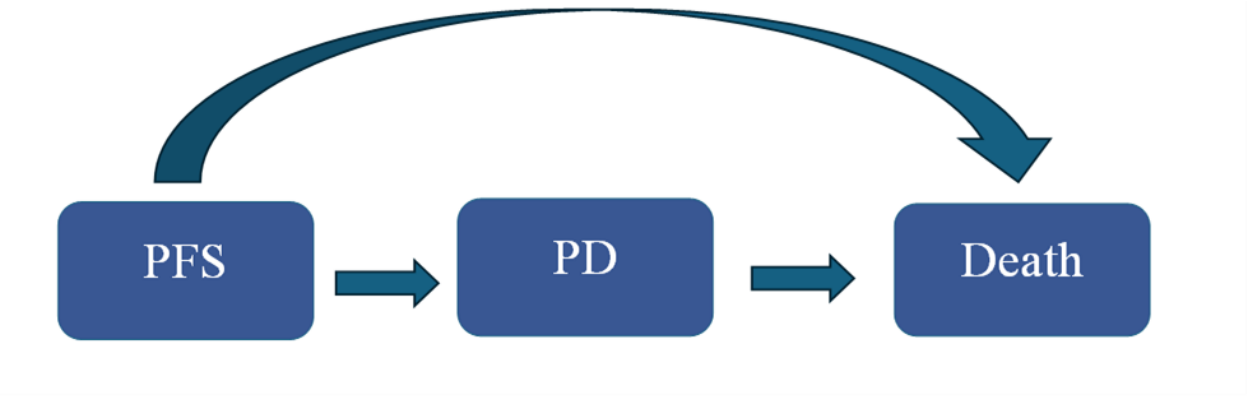
These findings may further inform healthcare providers, payers, and policymakers in optimizing first-line treatment strategies for patients with aNSCLC. From a cost-effectiveness perspective, CCT could be a more favorable option for patients with aNSCLC, particularly those with PD-L1 expression levels of ≥1% compared to PCT. Our study is among the first to compare the cost-effectiveness of CCT and PCT as first-line treatments for patients with aNSCLC, using updated follow-up clinical outcomes from three phase 3 clinical trials (EMPOWER-Lung 3, KEYNOTE-407, and KEYNOTE-189). [23, 38, 41] However, it is important to recognize some limitations. In the PSM, PFS and OS were assumed independent and extrapolated independently beyond the trial follow-up to ten years. Failure to account for dependencies between PFS and OS may affect the accuracy of extrapolated efficacy and undermine the validity of the results. Moreover, no clinical trial directly compared CCT and PCT, so any conclusions about the effectiveness and safety of these treatments' comparison should be taken cautiously. When indirectly comparing CCT and PCT, we relied solely on these clinical trial data, which might not

fully reflect real-world treatment variations and patient heterogeneity. Furthermore, assuming that the best supportive care was the second-line treatment might not accurately reflect actual clinical practices. In the subgroup analyses, since the EMPOWER-Lung 3 trial did not provide OS and PFS curves for CCT at different PD-L1 levels, we could not directly compare them to the PCT groups based on PD-L1 expression levels. Instead, we used an NMA to calculate the HRs for the subgroup comparisons, which might not accurately reflect the real treatment effects among subgroups. However, this approach was used in a study comparing the cost-effectiveness of pembrolizumab versus cemiplimab monotherapy for aNSCLC when OS and PFS curves were not available.[80] Finally, we were unable to differentiate between squamous and non-squamous patients at each level of PD-L1 expression due to the lack of such data in the EMPOWER-Lung 3 trial. This limitation underscores the necessity for future comprehensive analyses as additional data become available.

5. Conclusion

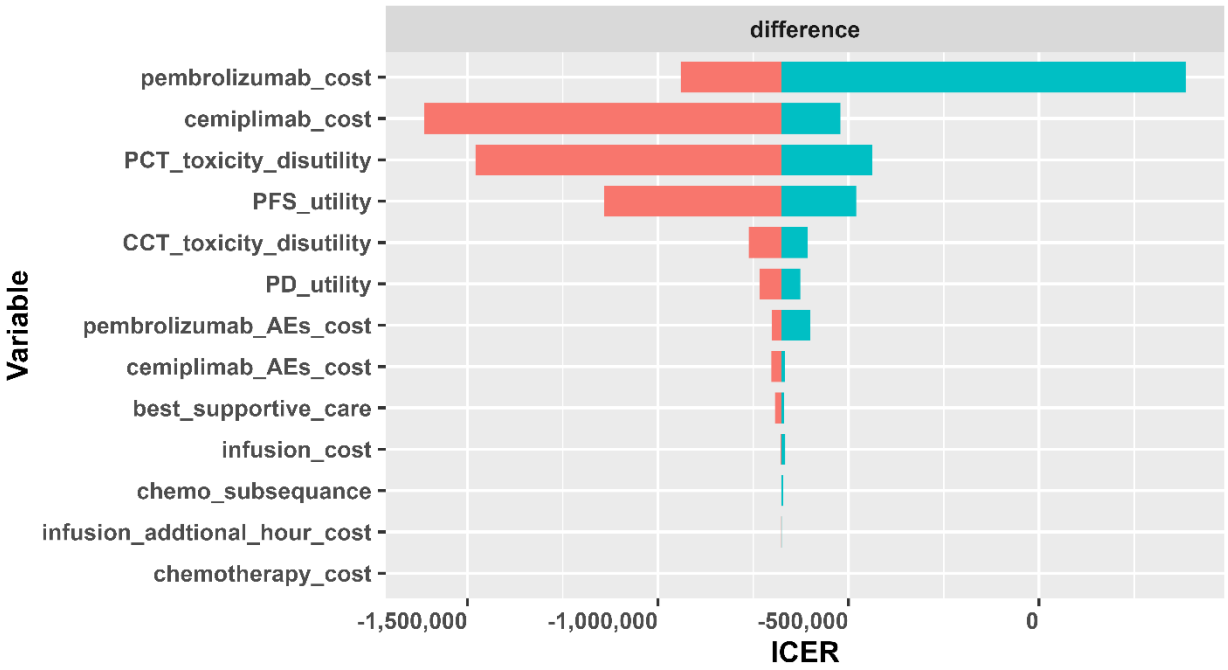
In conclusion, our findings suggested that, from the U.S. Medicare & Medicaid payer perspective, CCT is a dominant first-line treatment option for patients with aNSCLC compared to PCT, primarily due to its lower costs and better safety profile. Future research should reduce uncertainties by examining real-world data and exploring the subgroup and long-term effectiveness, the incidence of adverse events, and treatment costs.

Figure 1. Partitioned survival model



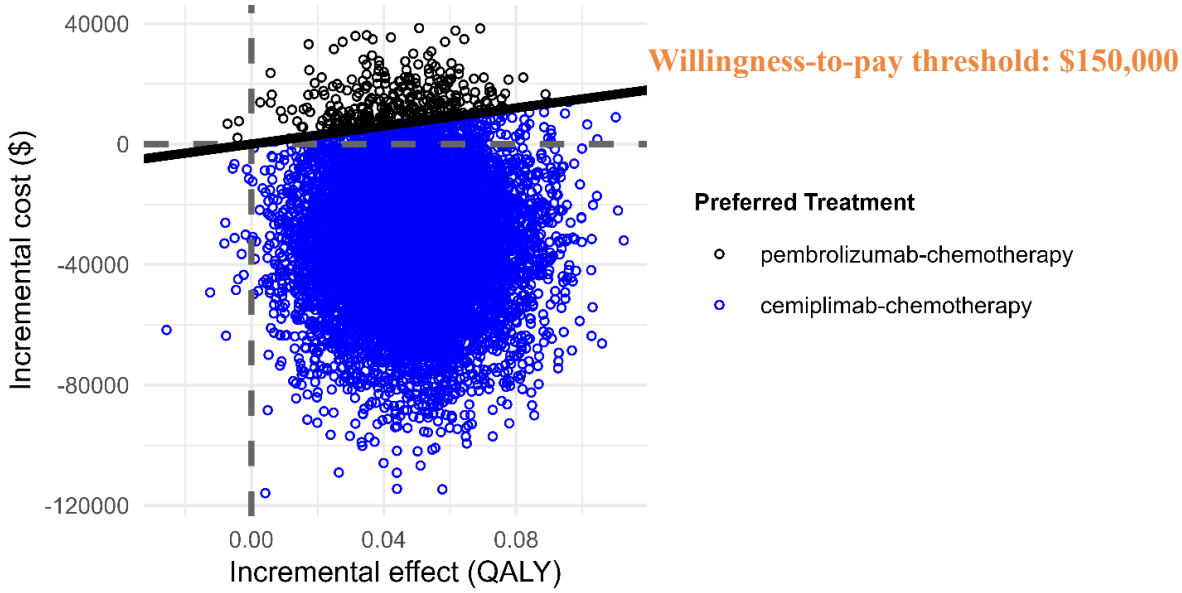
PD=progressed disease; PFS=progression-free survival.

Figure 2. Tornado plot of one-way deterministic sensitivity analysis of the ICER vs pembrolizumab plus chemotherapy



AE=adverse event; CCT=cemiplimab chemotherapy; ICER=incremental cost-effectiveness ratio; PCT=pembrolizumab chemotherapy; PD=progressed disease; PFS=progression-free survival

Figure 3. The probabilistic sensitivity analysis scatter plot



QALY=quality-adjusted life-year.

Table 1. Parameter imputation

Variable	Baseline value	Range		Distribution	Source
		Minimum	Maximum		
Pembrolizumab plus chemotherapy(squamous)					
OS	Shape=1.3442, scale = 18.1816	–	–	Log-logistic	KEYNOTE-407[38]
PFS	Shape=1.3840, scale = 8.9016	–	–	Log-logistic	KEYNOTE-407[38]
Pembrolizumab plus chemotherapy(nonsquamous)					
OS	Shape = 1.3597, scale = 21.7792	–	–	Log-logistic	KEYNOTE-189[23]
PFS	Log-mean = 2.296 log-standard deviation = 1.1705	–	–	Log-normal	KEYNOTE-189[23]
Cemiplimab plus chemotherapy					
OS	Log-mean = 3.0422 log-SD = 1.1295	–	–	Log-normal	EMPOWER-Lung 3[41]
PFS	Log-mean=2.2334, log-SD=1.0438	–	–	Log-normal	EMPOWER-Lung 3[41]
Drug price per Milligram, USD ($) [a]					
Cemiplimab	27.576	19.303	30.333	Gamma	ASP Drug Pricing Files[39]
Pembrolizumab	57.307	40.115	63.038	Gamma	ASP Drug Pricing Files [39]
Pemetrexed	3.617	2.532	3.979	Gamma	ASP Drug Pricing Files [39]
Paclitaxel	0.107	0.075	0.118	Gamma	ASP Drug Pricing Files [39]
Carboplatin	3.722	2.605	4.094	Gamma	ASP Drug Pricing Files [39]
Cisplatin	3.271	2.290	3.598	Gamma	ASP Drug Pricing Files [39]
Nab-paclitaxel	13.714	9.5998	15.086	Gamma	ASP Drug Pricing Files [39]
Mean Cost of AEs per patients, USD [ab]					
Cemiplimab plus chemotherapy	4,346.011	3042.208	4780.612	Gamma	Paul et al.[174] Nafees et al.[42] Wong et al.[130]

Pembrolizumab plus chemotherapy [c]	12,194.160	8535.912	13413.576	Gamma	Wong et al.[130] Insinga et al.[129]
Health utility					
PFS	0.754	0.679	0.829	Beta	Nafees et al.[42]
PD	0.180	0.162	0.198	Beta	Nafees et al.[42]
Disutility of AEs [d]					
Cemiplimab plus chemotherapy	0.0304	0.0273	0.033	Beta	Paul et al.[174] Nafees et al.[42]
Pembrolizumab plus chemotherapy [d]	0.127	0.114	0.140	Beta	Paul et al.[174] Nafees et al.[42]
Subsequence cost per cycle USD [a]	192.074	134.451	211.281	Gamma	ASP Drug Pricing Files [39]
Best supportive care per month USD [a]	1625.470	1137.829	1788.017	Gamma	Sheehan et al.[127]
Drug administration cost, USD					
First hour	141.140	98.798	155.254	Gamma	CMS Physician Fee Schedule
Additional hour	30.405	21.284	33.446	Gamma	CMS Physician Fee Schedule

[a]Costs are adjusted to 2024 USD based on the US Consumer Price Index.

[b]Calculated as an average cost of toxicity using the weighted probability of occurrence.

[c]Squamous and nonsquamous non–small cell lung cancer are weighted as 0.429 and 0.571 (same histology distribution in the EMPOWER-Lung 3 trial).

[d]Calculated as an average disutility of toxicity using the weighted probability of occurrence.

AE=adverse event; ASP=average sales price; OS=overall survival; nab=nanoparticle albumin-bound; PD=progressed disease; PFS=progression-free survival; USD=US dollar; CMS=Centers for Medicare & Medicaid Services

Table 2. Results of base-case and scenario analyses

	Treatment	Total cost, USD	Total QALYs	Incremental cost, USD	Incremental QALY	ICER, USD/QALY
Base-case	PCT	207,926	1.609	–	–	–
	CCT	175,247	1.657	−32,679	0.048	−675,304
Scenario 1	PCT	207,768	1.612	–	–	–
	CCT	175,247	1.657	−32,522	0.044	−731,180
Scenario 2	PCT	206,876	1.594	–	–	–
	CCT	175,078	1.655	−31,799	0.060	−528,262

CCT=cemiplimab chemotherapy; ICER=incremental cost-effectiveness ratio;
PCT=pembrolizumab chemotherapy; QALY=quality-adjusted life-year; USD=US dollar.

Chapter 5: Discussion and conclusion

Findings from this project provide new evidence on the effectiveness, safety, and cost-effectiveness of first-line ICI treatments for patients with mNSCLC. This chapter summarizes the key findings, discusses their clinical and policy implications, and outlines potential directions for future research.

Aim 1 of this dissertation focused on the comparative effectiveness of first-line individual ICI agents (pembrolizumab, nivolumab, and atezolizumab), ICI-Monotherapy versus ICI-Chemotherapy, and 4-cycle versus 6-cycle chemotherapy regimens within first-line ICI-Chemotherapy treatment. We found that first-line pembrolizumab was associated with a significant OS benefit compared to atezolizumab and nivolumab among older adults with mNSCLC. Among patients with squamous histology, OS differences between pembrolizumab and nivolumab were inconclusive. These findings support pembrolizumab as the preferred first-line ICI treatment for older patients with mNSCLC while underscoring the need for further investigation of nivolumab's effectiveness in squamous subgroups. In real-world clinical settings, findings from this study contribute to the advancement of standardized treatment guidelines and evidence-based decision-making for mNSCLC. Additionally, we observed that first-line ICI-Chemotherapy was associated with significantly improved OS compared to ICI-Monotherapy. Extending chemotherapy from 4 to 6 cycles within ICI-Chemotherapy regimens provided additional survival benefits. These results highlight the clinical importance of chemotherapy as a component of first-line ICI regimens in this population. However, due to the limited sample size, we did not assess the PP treatment effectiveness in the comparison of ICI agents within specific subgroups, such as histologic subtypes. Further research is warranted to validate the comparative effectiveness of ICIs among patients who adhered to their initial ICI

agents within these clinically relevant subgroups. In addition, our findings should be validated using electronic health record data, which can capture more detailed clinical information that is not available in the SEER-Medicare database, such as PD-L1 expression. Since the indications for ICI regimens vary by PD-L1 expression level, ICI-Chemotherapy regimens also warrant further evaluation and comparison with ICI-Monotherapy, stratified by the PD-L1 expression. Furthermore, the combination of nivolumab and ipilimumab, as well as newer approved ICI agents like cemiplimab, warrants further evaluation as additional data becomes available.[145] Lastly, our findings should be validated in broader patient populations beyond older adults to enhance generalizability.

In Aim 2, using the SEER-Medicare database, we found that the LASSO model outperformed other ML approaches, including RF, XGBoost, and SVM, in predicting endocrine-related irAEs among patients with mNSCLC. Key predictors identified by the LASSO model included pre-existing endocrine disorders, type 2 diabetes, use of atezolizumab, concurrent chemotherapy, and patient demographic factors. This study demonstrated the feasibility of using cancer registry-linked claims data and ML to predict endocrine-related irAEs. The consistent identification of clinically relevant risk factors provides valuable insights for risk stratification and supports proactive strategies to manage patients at higher risk of developing endocrine toxicities. Future research should incorporate additional clinically meaningful variables and apply time-to-event ML models to improve predictive performance. These approaches should also be extended to predict other irAEs, such as pneumonitis and gastrointestinal toxicities, as initially proposed in Aim 2.

In aim 3, our findings suggested that, from the U.S. Medicare & Medicaid payer perspective, CCT is a dominant first-line treatment option for patients with aNSCLC compared

to PCT, primarily due to its lower costs and better safety profile. This conclusion remained consistent in subgroup analyses among patients with PD-L1 expression levels ≥50% and 1%–49%. These results suggest that CCT could be a more cost-effective first-line option than PCT for patients with aNSCLC, particularly those with PD-L1 expression ≥1%. These findings may support payer decision-making by identifying more cost-effective first-line treatment strategies. However, as this study involved an indirect comparison across three clinical trials, differences in patient characteristics may limit the comparability of results, and the findings may not fully reflect real-world clinical practice. Future cost-effectiveness analyses should aim to reduce these uncertainties by utilizing real-world data to examine long-term treatment effectiveness, incidence of AEs, and treatment-related costs.

In summary, this dissertation employed a comprehensive approach—including comparative effectiveness analysis, AE risk prediction, and cost-effectiveness evaluation—to generate real-world evidence aimed at optimizing first-line ICI treatment for patients with mNSCLC. These findings contribute to the growing body of evidence supporting the use of ICIs, inform clinical and policy decision-making, and may help improve outcomes for patients receiving first-line ICI therapy.

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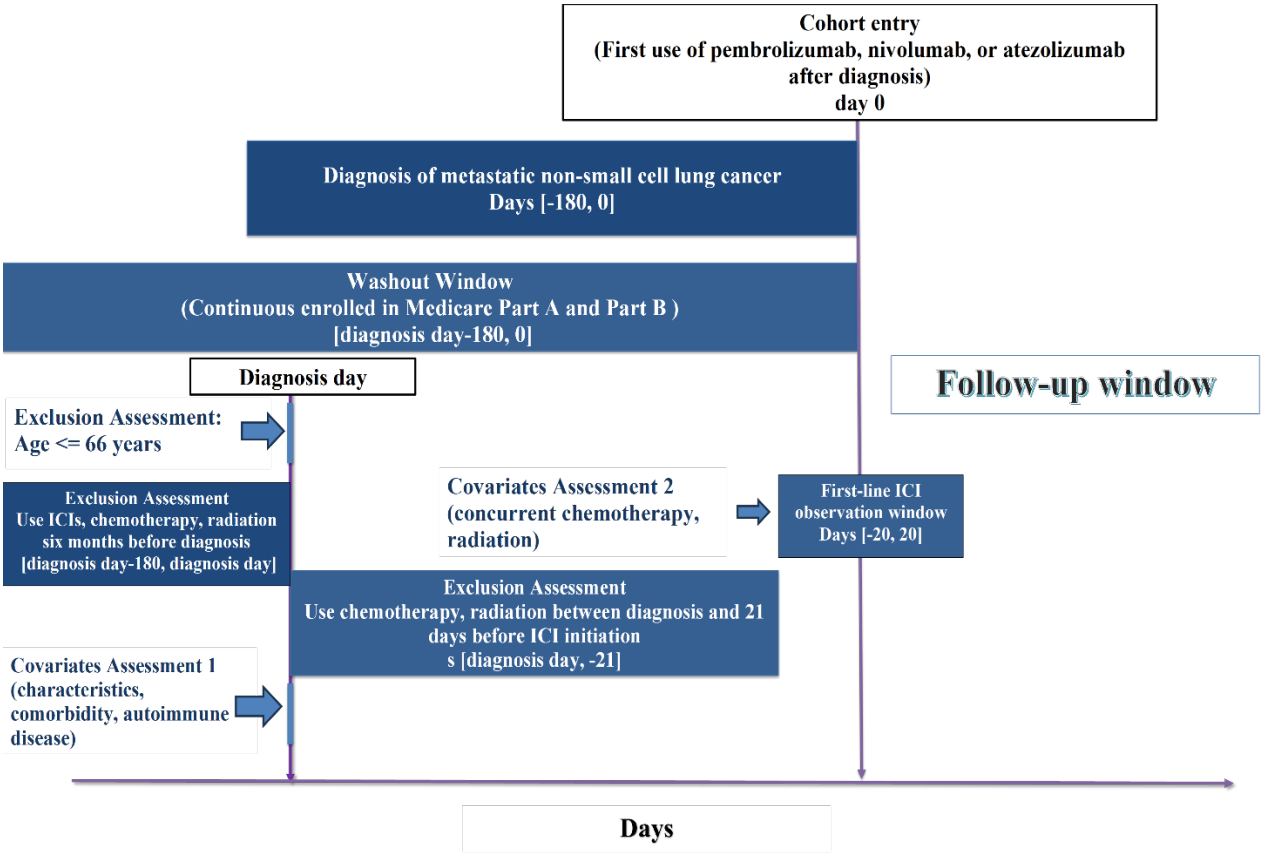
Appendix

Appendix for Aim 1.1 paper

Supplementary Figure 1. New user cohort design



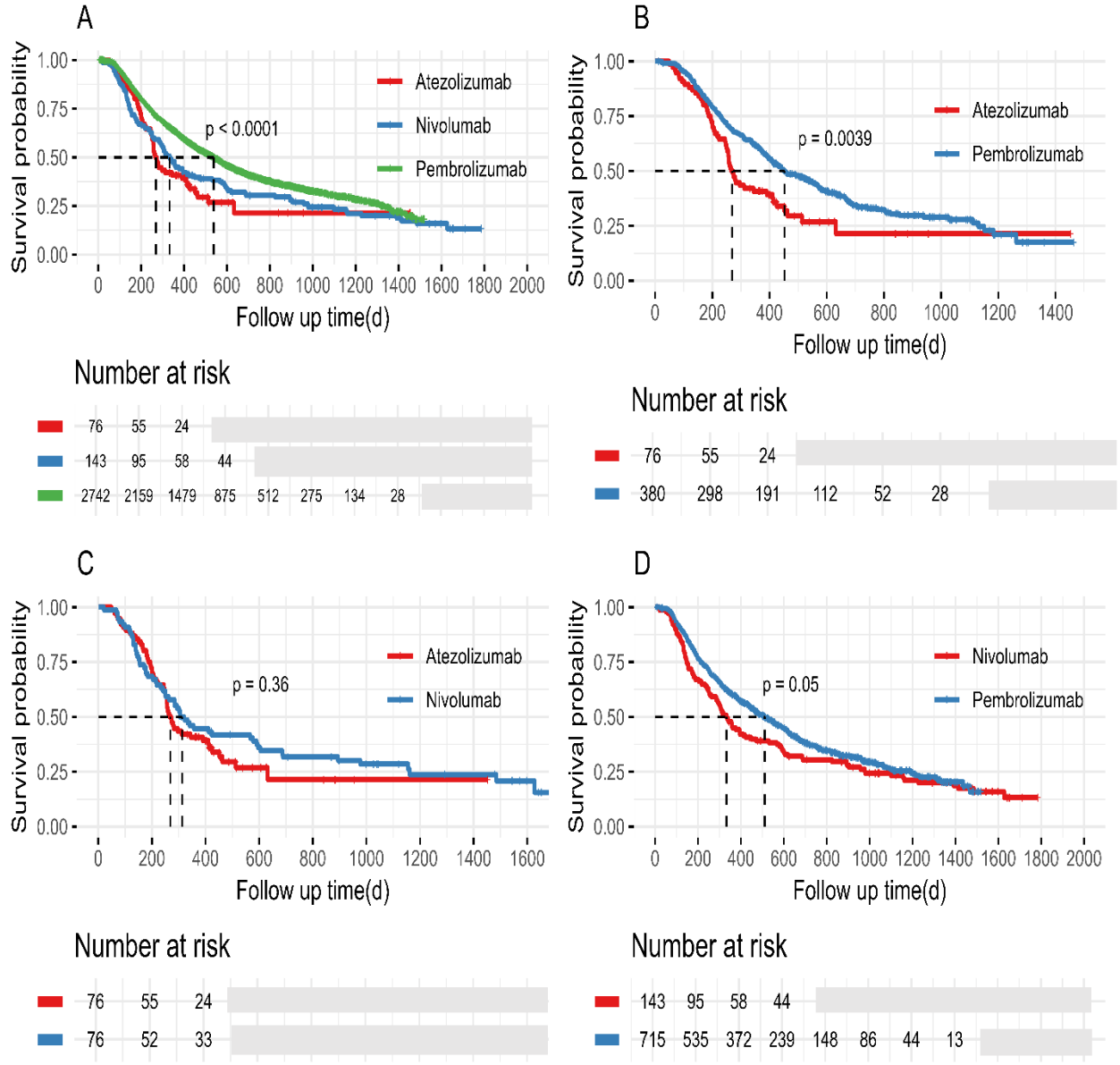
Supplementary Figure 2. Survival probabilities of first-line pembrolizumab, nivolumab, and atezolizumab in patients with mNSCLC in sensitivity analyses before and after propensity score matching

A. Survival probabilities of atezolizumab (N=76), nivolumab (N=143), and pembrolizumab (N=2742)

B. Survival probabilities of atezolizumab (N=76) and pembrolizumab (N=380) after propensity score matching

C. Survival probabilities of atezolizumab (N=76) and nivolumab (N=76) after propensity score matching

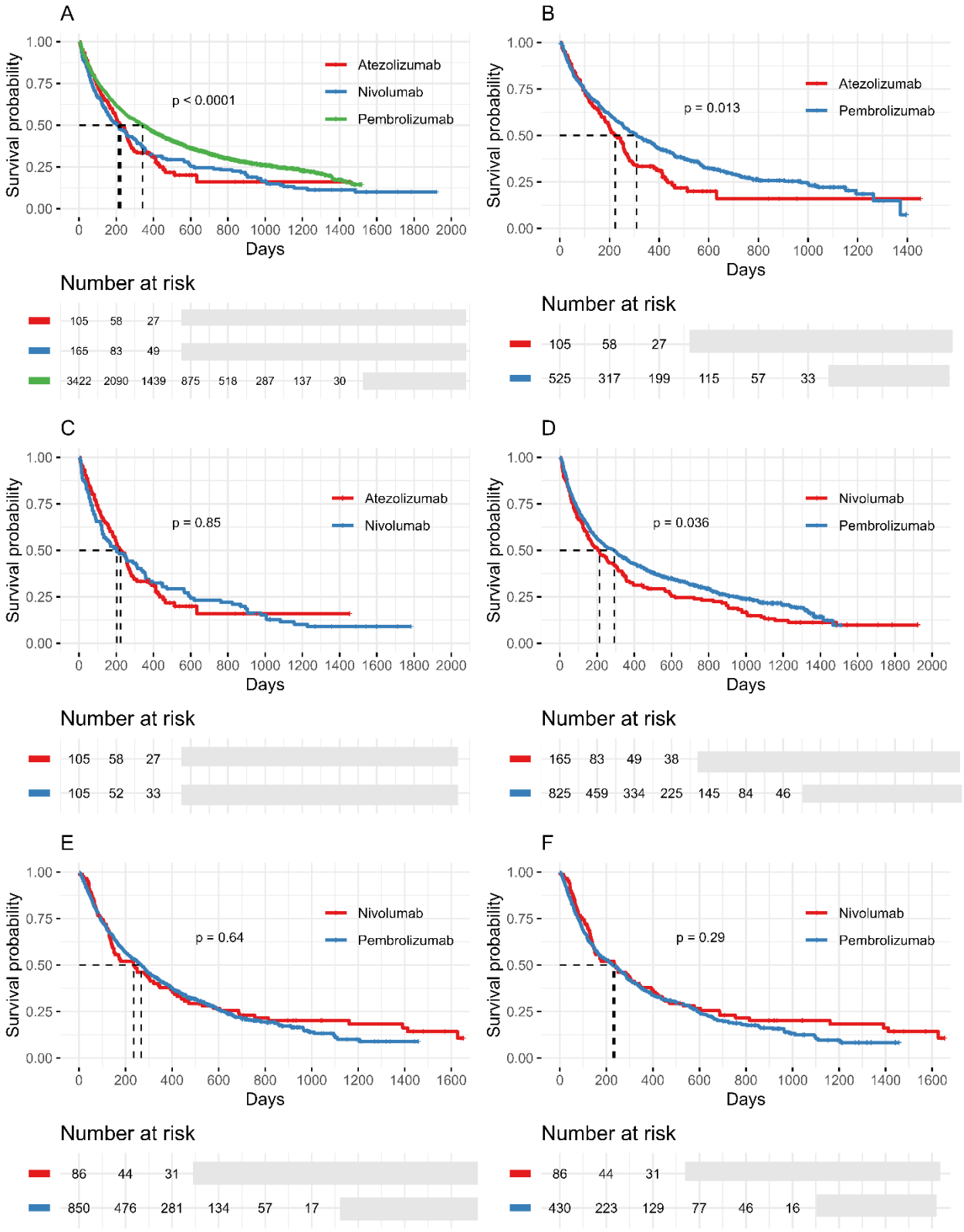
D. Survival probabilities of nivolumab (N=143) and pembrolizumab (N=715) after propensity score matching



Suppressed due to a sample size of Ns < 11 or changes in the number of individuals at risk between time points of Ns < 11

Supplementary Figure 3. Survival probabilities of first-line pembrolizumab, nivolumab, and atezolizumab in patients with nonsquamous and squamous mNSCLC before and after propensity score matching

A. Survival probabilities of atezolizumab (N=105), nivolumab (N=165), and pembrolizumab N=3422) in patients with nonsquamous mNSCLC
B. Survival probabilities of atezolizumab (N=105) and pembrolizumab (N=525) in patients with nonsquamous mNSCLC after propensity score matching
C. Survival probabilities of atezolizumab (N=105) and nivolumab (N=105) in patients with nonsquamous mNSCLC after propensity score matching
D. Survival probabilities of nivolumab (N=165) and pembrolizumab (N=825) in patients with nonsquamous mNSCLC after propensity score matching
E. Survival probabilities of nivolumab (N=86) and pembrolizumab (N=850) in patients with squamous mNSCLC
F. Survival probabilities of nivolumab (N=86) and pembrolizumab (N=430) in patients with squamous mNSCLC after propensity score matching



Suppressed due to a sample size of Ns < 11 or changes in the number of individuals at risk between time points of Ns < 11

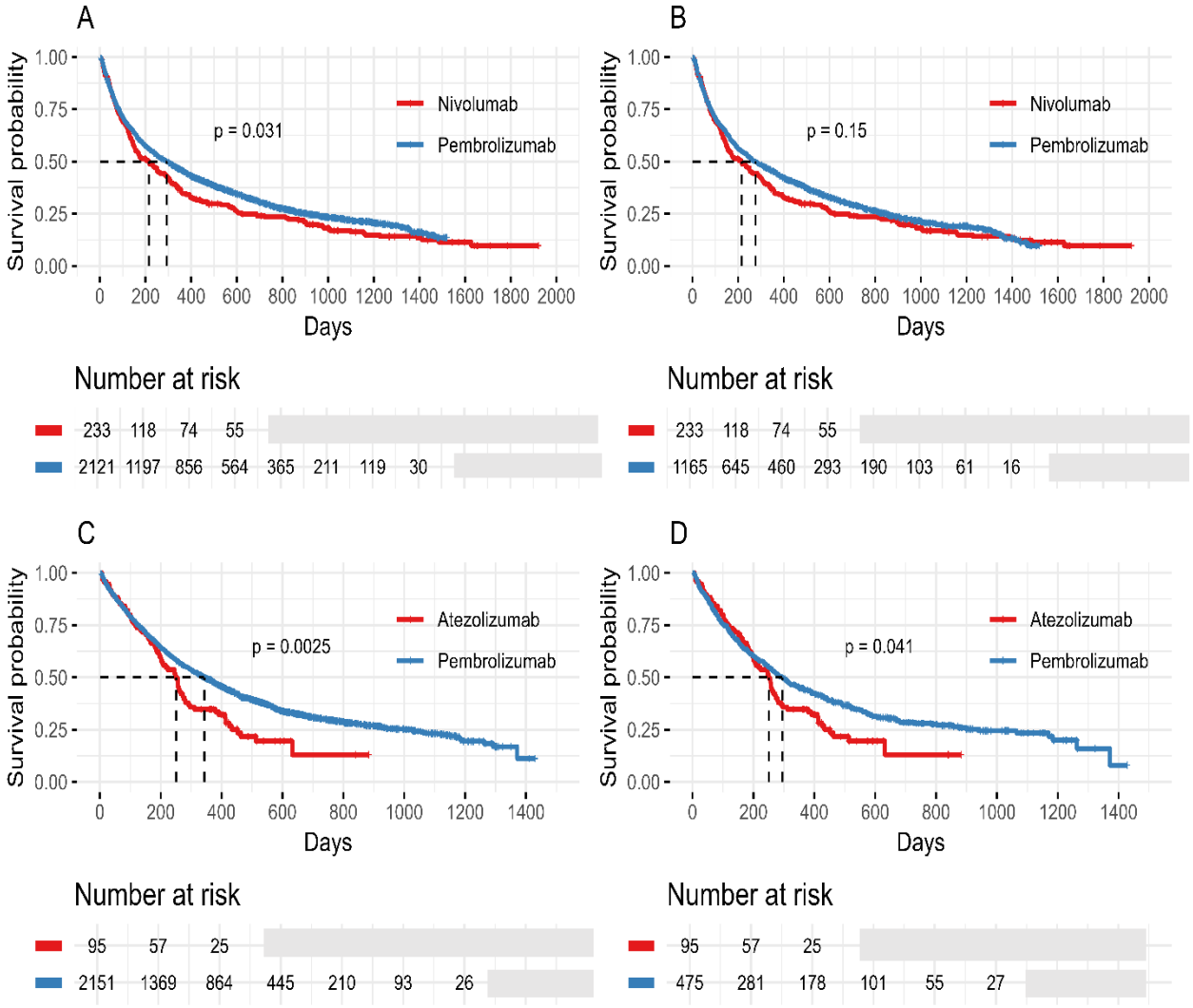
Supplementary Figure 4. Survival probabilities of first-line pembrolizumab-monotherapy, nivolumab-monotherapy, pembrolizumab-chemotherapy, and atezolizumab-chemotherapy in patients with mNSCLC before and after propensity score matching

A. Survival probabilities of nivolumab-monotherapy (N=233) and pembrolizumab-monotherapy (N=2121) in patients with mNSCLC

B. Survival probabilities of nivolumab-monotherapy (N=233) and pembrolizumab-monotherapy (N=1165) in patients with mNSCLC after propensity score matching

C. Survival probabilities of atezolizumab-chemotherapy (N=95) and pembrolizumab-chemotherapy (N=2151) in patients with mNSCLC

D. Survival probabilities of atezolizumab-chemotherapy (N=95) and pembrolizumab-chemotherapy (N=475) in patients with mNSCLC after propensity score matching



Suppressed due to a sample size of Ns < 11 or changes in the number of individuals at risk between time points of Ns < 11

Supplementary Table 1. ICD-O-3 codes for mNSCLC and medical codes for ICI, chemotherapy, and radiation treatment

Lung cancer ICD-O-3	C340-C343,C348-C349	
Histology ICD-O-3	Squamous	8010/3, 8012/3, 8020/3, 8046/3, 8050/3, 8051/3, 8140/3, 8141/3, 8143/3, 8147/3, 8250-8255/3, 8260/3, 8310/3,8430/3, 8480/3, 8481/3, 8490/3, 8560/3, and 8571-8575/3
	Non-squamous	8052/3, 8070-8083/3, 8570/3
ICI HCPCS	Atezolizumab	J9022, C9483
	Nivolumab	J9299, C9453
	Pembrolizumab	J9271, C9027
	Ipilimumab	J9228, C9284
	Durvalumab	J9173, C9492
	Cemiplimab	J9119
Chemotherapy ICD-9, ICD-10	ICD9	Diagnostic: V58.1, Procedure:99.25
	ICD10	Diagnostic: Z51.11, Procedure: 3E03305, 3E04305, XW03351, XW033B3, XW033C3, XW04351, XW043B3, XW043C3
Chemotherapy HCPCS	Carboplatin	J9045
	Cisplatin	C9418, J9060, J9062
	Docetaxel	J9170, J9171
	Paclitaxel	C9127, C9431, J9265, J9267, J9264
	Pemetrexed	C9213, J9304, J9305
	Gemcitabine	J9201, J9198
	Other HCPCS codes related to the chemotherapy*	96400, 96401, 96402, 96405, 96406, 96408, 96409, 96410, 96411, 96412, 96413, 96414, 96415, 96416, 96417, 96420, 96422, 96423, 96425, 96440, 96445, 96446, 96450, 96499, 96520, 96521, 96522, 96523, 96530, 96542, 96545, 96549, Q0083, Q0084, Q0085, Q2017, Q2024, S0087, S0088
Radiation	ICD-9codes	Diagnostic: V58.0, V66.1, V67.1, Procedure: 92.2, 92.20-92.29, 92.3, 92.30-92.33, 92.39, 92.4, 92.40, 92.41
	ICD-10 codes	Diagnostic: Z510, Procedure: 0HHT01Z, 0HHT31Z, 0HHT71Z, 0HHT81Z, 0HHTX1Z, 0HHU01Z, 0HHU31Z, 0HHU71Z, 0HHU81Z, 0HHUX1Z, 0HHV01Z, 0HHV31Z, 0HHV71Z, 0HHV81Z, 0HHVX1Z, 0HHW01Z, 0HHW31Z, 0HHW71Z, 0HHW81Z, 0HHWX1Z, 0HHX01Z, 0HHX31Z, 0HHX71Z, 0HHX81Z, 0HHXX1Z
	HCPCS	HCPCS/CPT: 76370, 76950, 76965, 77261-77263, 77280, 77285, 77290, 77293, 77295, 77299-77301, 77305-77307, 77310, 77315-77318, 77321, 77326-

		77328, 77331-77334, 77336, 77338, 77370-77373, 77385-77387, 77399, 77401-77404, 77406-77409, 77411-77414, 77416-77418, 77421-77425, 77427, 77431, 77432, 77435, 77469, 77470, 77499, 77520, 77522, 77523, 77525, 77750, 77761-77763, 77767, 77768, 77770, 77771, 77772, 77776-77778, 77781-77790, 77799, 0182T, C1325, C1348, C1350, C1700- C1712, C1715-C1720, C1728, C1790-C1806, C2616, C2632, C2633, C9120, C9216, C9430, C9714, C9715, G0174, G0178, G0179, G0251, G0256, G0261, G0273, G0274, G0338-G0340, J0128, J1675, J1950, J3315, J9165, J9202, J9217-J9219, J9225, J9226, Q2020, S0165, S0175, S0189, S9560

MNSCLC: metastatic non-small cell lung cancer; ICI: immune checkpoint inhibitor; HCPCS: Healthcare Common Procedure Coding System; ICD-9: International Classification of Diseases Nine Version; ICD-10: International Classification of Diseases Ten Version; NDC: National Drug Code

*These codes are used in washout cleaning but not first-line treatment identification.

Supplementary Table 2. Autoimmune disease and ICD-9-CM/ICD-10-CM codes

Organ system	ICD-9 codes	ICD-10 codes
Dermatologic	693.0 698.8 697.0 709.00, 709.01, 709.09 694.5 695.13, 695.14	L27.0, L27.1 L29.8, L29.9 L43.x, L44.3, L66.1 L80, L81.8, L81.9 L12.0 L51.1, L51.3
Hematologic	285.3, 285.8, 285.9284.x, 283.x 287.3, 287.31, 287.8, 287.9, 287.31, 287.32, 287.4, 287.49, 287.5287.8, 287.9 288.00, 288.03, 288.09 288.4, 288.5x, 288.8, 288.9	D59.x, D61.x, D60.x, D64.2, D64.3, D64.8 D69.3, D69.41, D69.49, D69.59, D69.6 D72.1, D72.81, D72.810, D72.818, D72.819, D70.9, D70.4, D70.2, D76.1, D76.3
Pulmonary	508.8, 508.9, 486.x, 516.3x, 516.9	J84.11x, J70.9, J70.8, J70.2, J70.3, J70.4, J18.9, J84.89, J84.9
Liver	573.3, 790.5	K71, R74.8, K75.4, K75.9, R94.5
Gastrointestinal	558.2, 558.3, 558.4, 558.9, 555, 556.8, 556.9 577.0 528.x	K52.1, K52.29, K52.3, K52.9, K52.89, K53.82 K85.x K12.30, K12.31
Endocrine	244.3, 244.8, 244.9 242.x 250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93 250.11, 250.13 253.8 255.41	E03.2, E03.8, E03.9 E05.x E09.x, E10.x, E13 E10.1 E23.6 E27.1, E27.3, E27.4
Renal	584.x 591.10, 591.11, 583.89 580.x, 581.x, 583.x	N17.x N10.x, N12.x, N14.1, N14.2 N00.x, N01.x, N04.x, N05.x N06.x,
Cardiac	427.x 410.x 422.x, 429.x 420.x, 423.x 425.4, 425.9	I48.x, I47.x, I49.x, I46.x I21.x I40.x, I51.4, I51.8, I51.9 I30.x I31.4, I31.8-9 I42.0, I42.7, I42.9

Musculoskeletal	710.3, 710.4 714.x 729.1 725, 446.5 729.2	M33 M05, M06, M08.0, M08.2, M08.3, M08.4, M08.8, M08.9, M12.0 M79.1 M35.5, M31.5, M31.6 M79.2
Central Nervous System	047.9, 322.9 323.8, 323.81, 323.82, 323.7, 323.71, 323.72, 323.9 357.0 358.0 357.89	G03.9, A87.9 G92, G04.81, G04.89, G04.90, G04.91 G61.0 G70.0 G64

Supplementary Table 3. Patient characteristics in atezolizumab and pembrolizumab comparison after propensity score matching

	Immune Checkpoint Inhibitor		
Characteristic	**Atezolizumab N = 112[1]**	**Pembrolizumab N = 560[1]**	**Standardized mean difference**
Age (years)	73.0 (69.0, 80.0)	74.0 (70.0, 78.0)	0.055
Geographic Region			0.053
Midwest	–	23 (4.1%)	
Northeast	>34 (>30.4%)*	194 (34.6%)	
South	31 (27.7%)	153 (27.3%)	
West	36 (32.1%)	190 (33.9%)	
Metropolitan Status			0.011
Metropolitan	100 (89.3%)	498 (88.9%)	
Nonmetropolitan	12 (10.7%)	62 (11.1%)	
Sex			0.007
Female	41 (36.6%)	207 (37.0%)	
Male	71 (63.4%)	353 (63.0%)	
Race			0.005
Non-White	14 (12.5%)	69 (12.3%)	
White	98 (87.5%)	491 (87.7%)	
Yost index state quintiles (area level SES[2] deprivation)			0.080
Group 1, lowest SES	–	>45 (>8.0%)	
Group 2, low-middle SES	20 (17.9%)	107 (19.1%)	
Group 3, middle SES	20 (17.9%)	91 (16.3%)	

Group 4, high-middle SES	28 (25.0%)	146 (26.1%)	
Group 5, highest SES	32 (28.6%)	160 (28.6%)	
Unknown, blank	–	–	
Charlson Comorbidity Index			0.009
>=2	41 (36.6%)	205 (36.6%)	
0	45 (40.2%)	227 (40.5%)	
1	26 (23.2%)	128 (22.9%)	
Tumor Histology			0.007
nonsquamous	>100 (>89.2%)*	524 (93.6%)	
squamous	–	36 (6.4%)	
Autoimmune Disease History			0.010
No	72 (64.3%)	350 (62.5%)	
Yes	40 (35.7%)	210 (37.5%)	
Chemotherapy			0.010
No	17 (15.2%)	87 (15.5%)	
Yes	95 (84.8%)	473 (84.5%)	
Radiation Therapy			0.024
No	92 (82.1%)	465 (83.0%)	
Yes	20 (17.9%)	95 (17.0%)	
Time to Treatment Initiation (days)	49.5 (37.5, 67.0)	51.0 (38.0, 68.0)	0.037

[1]Median (Q1, Q3); n (%)

[2]SES = socioeconomic status

–: suppressed due to cell size < 11

*: coarsened another category to suppress cells with size < 11 adequately

Supplementary Table 4. Patient characteristics in atezolizumab and nivolumab comparison after propensity score matching

	Immune Checkpoint Inhibitor		
Characteristic	**Atezolizumab N = 112[1]**	**Nivolumab N = 112[1]**	**Standardized mean difference**
Age (years)	73.0 (69.0, 80.0)	78.0 (73.0, 82.5)	0.462
Geographic Region			0.348
Midwest	–	–	
Northeast	>34 (>30.4%)*	>34 (>30.4%)*	
South	31 (27.7%)	20 (17.9%)	
West	36 (32.1%)	39 (34.8%)	
Metropolitan Status			0.280
Metropolitan	100 (89.3%)	>101 (>90.2%)*	
Nonmetropolitan	12 (10.7%)	–	
Sex			0.056
Female	41 (36.6%)	38 (33.9%)	
Male	71 (63.4%)	74 (66.1%)	
Race			0.027
Non-White	14 (12.5%)	13 (11.6%)	
White	98 (87.5%)	99 (88.4%)	
Yost index state quintiles (area level SES[2] deprivation)			0.163
Group 1, lowest SES	–	–	
Group 2, low-middle SES	20 (17.9%)	20 (17.9%)	
Group 3, middle SES	20 (17.9%)	26 (23.2%)	

Group 4, high-middle SES	28 (25.0%)	28 (25.0%)	
Group 5, highest SES	32 (28.6%)	29 (25.9%)	
Unknown, blank	–	–	
Charlson Comorbidity Index			0.229
>=2	41 (36.6%)	40 (35.7%)	
0	45 (40.2%)	55 (49.1%)	
1	26 (23.2%)	17 (15.2%)	
Tumor Histology			0.069
nonsquamous	>101 (>90.2%)*	>101 (>90.2%)*	
squamous	–	–	
Autoimmune Disease History			0.074
No	72 (64.3%)	68 (60.7%)	
Yes	40 (35.7%)	44 (39.3%)	
Chemotherapy			2.042
No	17 (15.2%)	97 (86.6%)	
Yes	95 (84.8%)	15 (13.4%)	
Radiation Therapy			0.177
No	92 (82.1%)	99 (88.4%)	
Yes	20 (17.9%)	13 (11.6%)	
Time to Treatment Initiation (days)	49.5 (37.5, 67.0)	61.5 (43.0, 87.0)	0.410

[1]Median (Q1, Q3); n (%)

[2]SES = socioeconomic status

–: suppressed due to cell size < 11

*: coarsened another category to suppress cells with size < 11 adequately

Supplementary Table 5. Patient characteristics in nivolumab and pembrolizumab comparison after propensity score matching

	Immune Checkpoint Inhibitor		
Characteristic	**Nivolumab N = 251[1]**	**Pembrolizumab N = 1,255[1]**	**Standardized mean difference**
Age (years)	79.0 (73.0, 84.0)	79.0 (74.0, 84.0)	0.001
Geographic Region			0.942
Midwest	17 (6.8%)	86 (6.9%)	
Northeast	77 (30.7%)	408 (32.5%)	
South	66 (26.3%)	327 (26.1%)	
West	91 (36.3%)	434 (34.6%)	
Metropolitan Status			0.003
Metropolitan	224 (89.2%)	1119 (89.2%)	
Nonmetropolitan	27 (10.8%)	136 (10.8%)	
Sex			0.043
Female	119 (47.4%)	622 (49.6%)	
Male	132 (52.6%)	633 (50.4%)	
Race			0.038
Non-White	22 (8.8%)	97 (7.7%)	
White	229 (91.2%)	1,158 (92.3%)	
Yost index state quintiles (area level SES[2] deprivation)			0.050
Group 1, lowest SES	22 (8.8%)	110 (8.8%)	
Group 2, low-middle SES	43 (17.1%)	206 (16.4%)	
Group 3, middle SES	57 (22.7%)	280 (22.3%)	

Group 4, high-middle SES	61 (24.3%)	295 (23.5%)	
Group 5, highest SES	57 (22.7%)	311 (24.8%)	
Unknown, blank	11 (4.4%)	53 (4.2%)	
Charlson Comorbidity Index			0.012
>=2	87 (34.7%)	428 (34.1%)	
0	101 (40.2%)	511 (40.7%)	
1	63 (25.1%)	316 (25.2%)	
Tumor Histology			0.041
nonsquamous	165 (65.7%)	849 (67.6%)	
squamous	86 (34.3%)	406 (32.4%)	
Autoimmune Disease History			0.003
No	155 (61.8%)	773 (61.6%)	
Yes	96 (38.2%)	482 (38.4%)	
Chemotherapy			0.012
No	233 (92.8%)	1,169 (93.1%)	
Yes	18 (7.2%)	86 (6.9%)	
Radiation Therapy			0.051
No	218 (86.9%)	1,111 (88.5%)	
Yes	33 (13.1%)	144 (11.5%)	
Time to Treatment Initiation (days)	61.0 (43.0, 91.0)	61.0 (44.0, 85.0)	0.079

[1]Median (Q1, Q3); n (%)

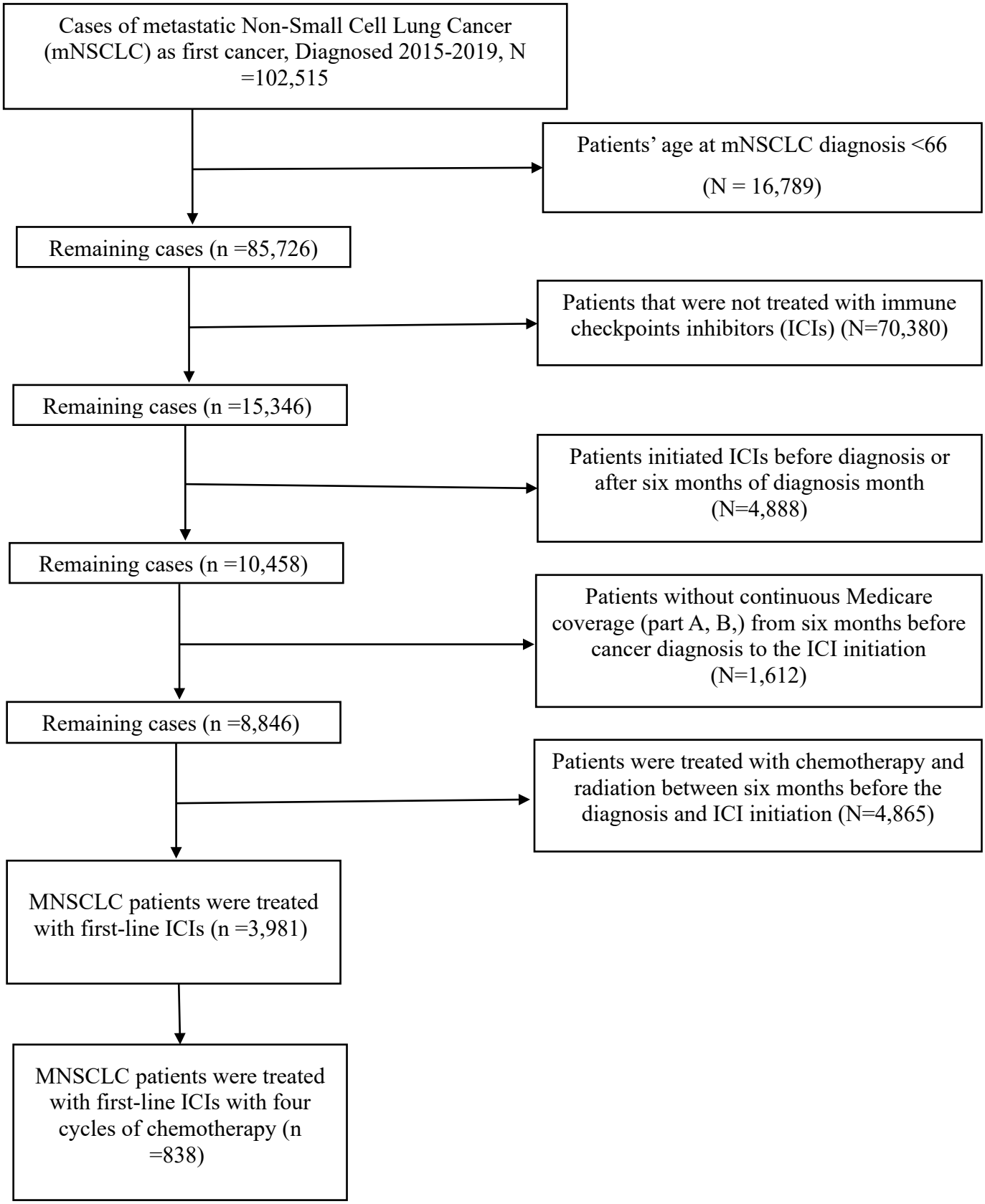
[2]SES = socioeconomic status

–: suppressed due to cell size < 11

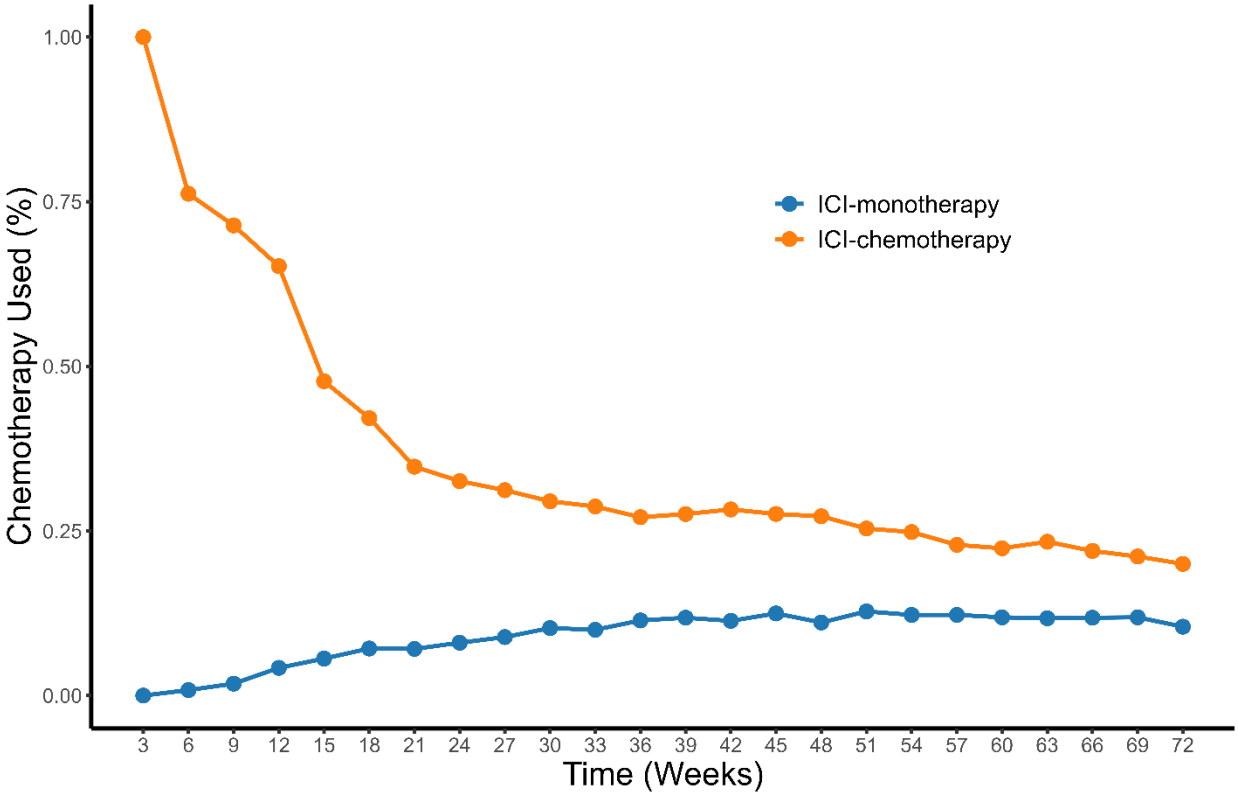
*: coarsened another category to suppress cells with size < 11 adequately

Appendix for Aim 1.2 paper

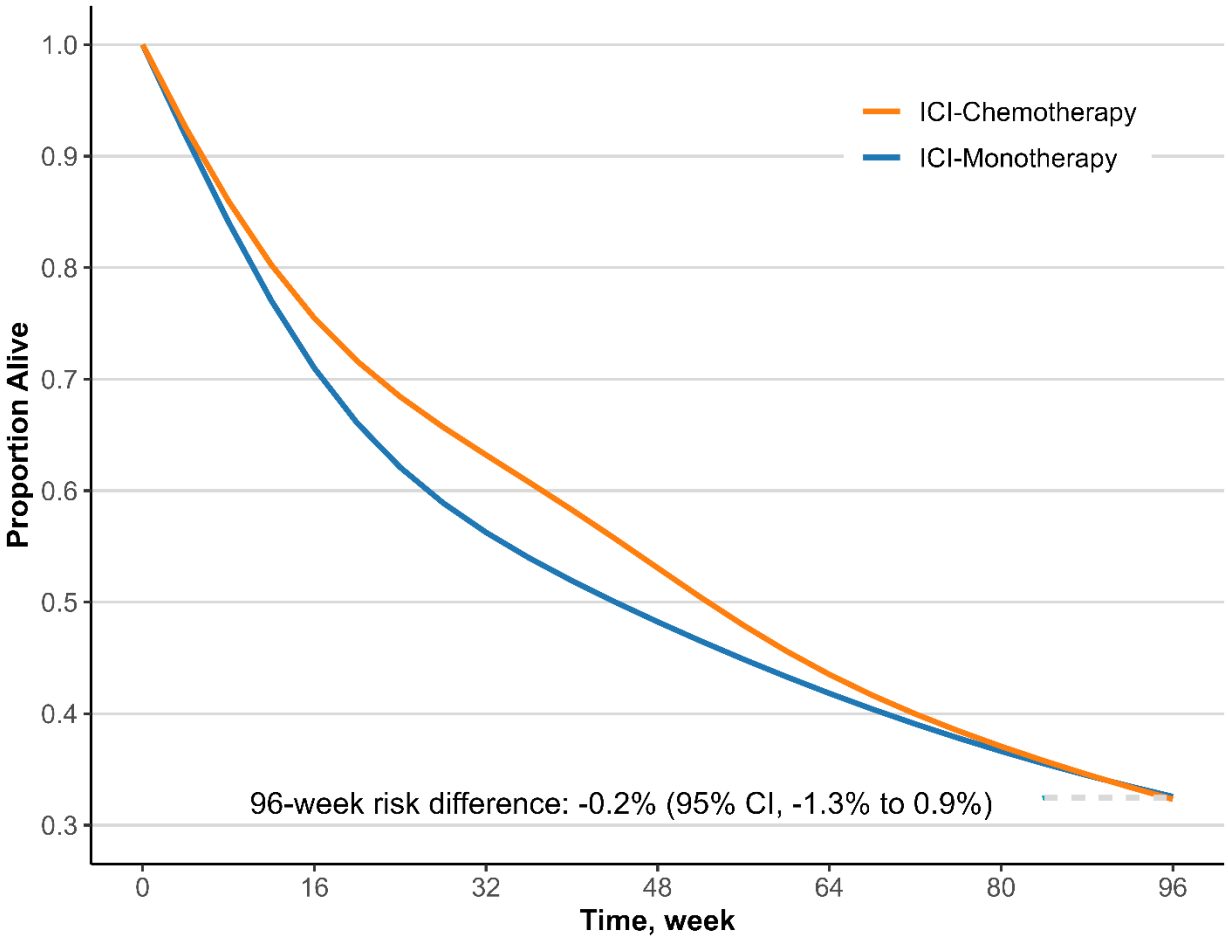
Supplementary Figure 1. Flowchart of patient inclusion and exclusion



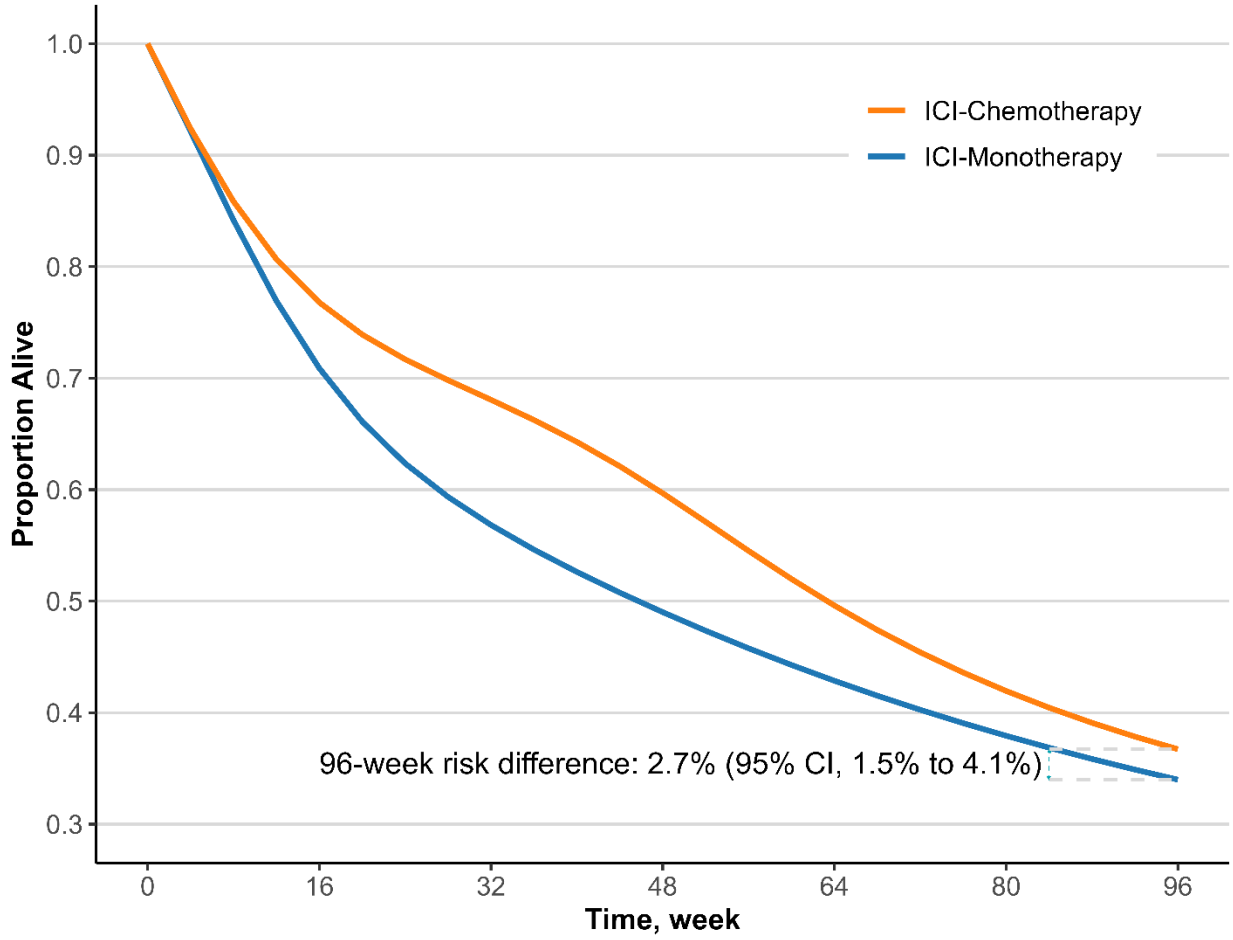
Supplementary Figure 2. Chemotherapy utilization in first-line ICI–Chemotherapy and ICI–Monotherapy groups among Medicare beneficiaries with metastatic non–small cell lung cancer



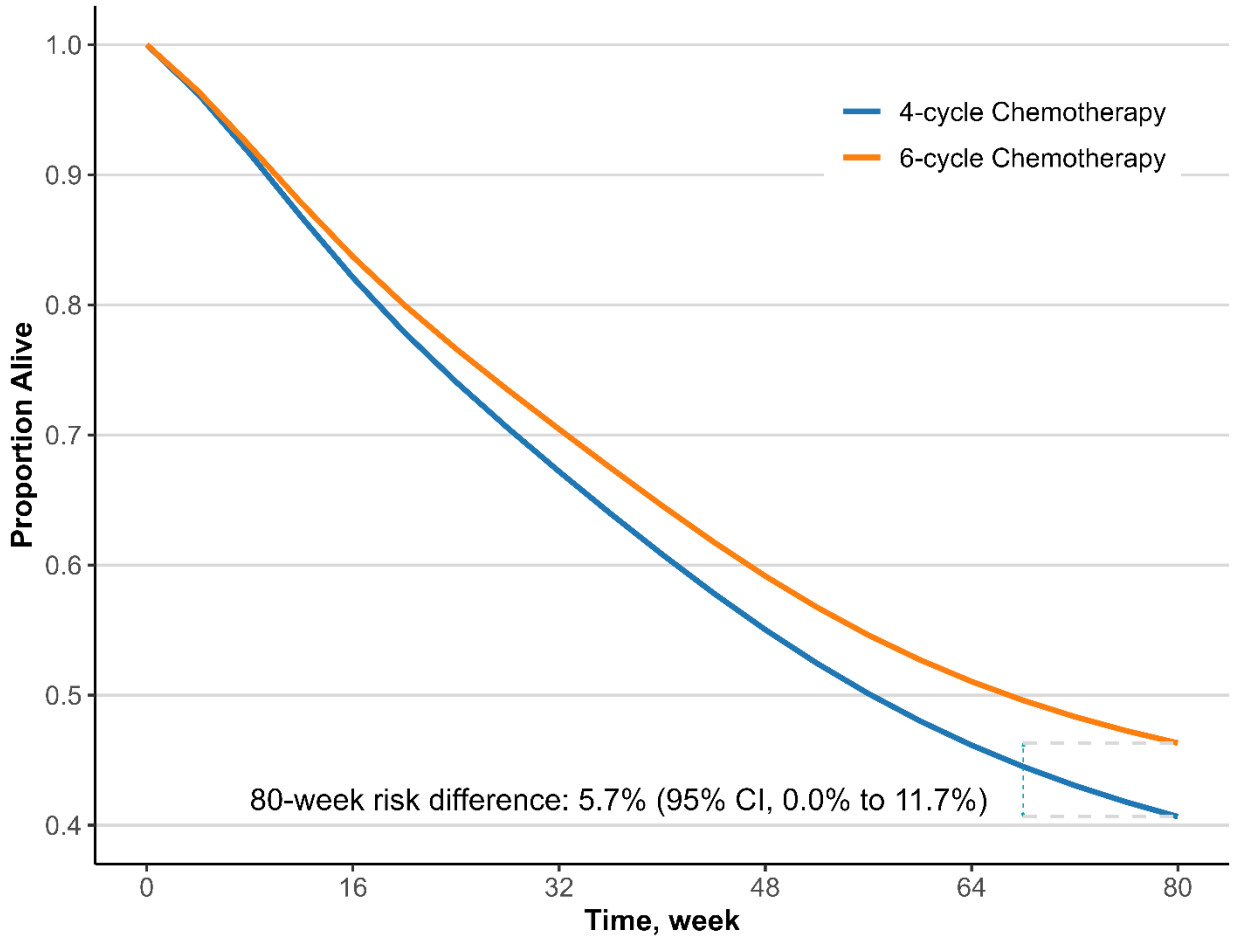
Supplementary Figure 3. Sensitivity analysis survival curves from the intention-to-treat analysis of the emulated target trial comparing first-line ICI-Chemotherapy vs. ICI-Monotherapy in metastatic non–small cell lung cancer



Supplementary Figure 4. Sensitivity analysis survival curves from the per-protocol analysis of first-line ICI–Chemotherapy vs. ICI–Monotherapy for metastatic non–small cell lung cancer



Supplementary Figure 5. Sensitivity analysis survival curves comparing 4-cycle vs. 6-cycle chemotherapy in the first-line ICI–Chemotherapy regimen for metastatic non–small cell lung cancer



Supplementary Table 1. ICD-O-3 codes for mNSCLC and medical codes for ICI, chemotherapy, and radiation treatments

Lung cancer ICD-O-3	C340-C343,C348-C349	
Histology ICD-O-3	Squamous	8010/3, 8012/3, 8020/3, 8046/3, 8050/3, 8051/3, 8140/3, 8141/3, 8143/3, 8147/3, 8250-8255/3, 8260/3, 8310/3,8430/3, 8480/3, 8481/3, 8490/3, 8560/3, and 8571-8575/3
	Non-squamous	8052/3, 8070-8083/3, 8570/3
ICI HCPCS	Atezolizumab	J9022, C9483
	Nivolumab	J9299, C9453
	Pembrolizumab	J9271, C9027
	Ipilimumab	J9228, C9284
	Durvalumab	J9173, C9492
	Cemiplimab	J9119
Chemotherapy	ICD9	Diagnostic: V58.1, Procedure:99.25
	ICD10	Diagnostic: Z51.11, Procedure: 3E03305, 3E04305, XW03351, XW033B3, XW033C3, XW04351, XW043B3, XW043C3
Chemotherapy HCPCS	Carboplatin	J9045
	Cisplatin	C9418, J9060, J9062
	Docetaxel	J9170, J9171
	Paclitaxel	C9127, C9431, J9265, J9267, J9264
	Pemetrexed	C9213, J9304, J9305
	Gemcitabine	J9201, J9198
Radiation	ICD-9codes	Diagnostic: V58.0, V66.1, V67.1, Procedure: 92.2, 92.20-92.29, 92.3, 92.30-92.33, 92.39, 92.4, 92.40, 92.41
	ICD-10 codes	Diagnostic: Z510, Procedure: 0HHT01Z, 0HHT31Z, 0HHT71Z, 0HHT81Z, 0HHTX1Z, 0HHU01Z, 0HHU31Z, 0HHU71Z, 0HHU81Z, 0HHUX1Z, 0HHV01Z, 0HHV31Z, 0HHV71Z, 0HHV81Z, 0HHVX1Z, 0HHW01Z, 0HHW31Z, 0HHW71Z, 0HHW81Z, 0HHWX1Z, 0HHX01Z, 0HHX31Z, 0HHX71Z, 0HHX81Z, 0HHXX1Z
	HCPCS/CPT	76370, 76950, 76965, 77261-77263, 77280, 77285, 77290, 77293, 77295, 77299-77301, 77305-77307, 77310, 77315-77318, 77321, 77326-77328, 77331-77334, 77336, 77338, 77370-77373, 77385-77387, 77399, 77401-77404, 77406-77409, 77411-77414, 77416-77418, 77421-77425, 77427, 77431, 77432, 77435, 77469, 77470, 77499, 77520, 77522, 77523, 77525, 77750, 77761-77763, 77767, 77768, 77770, 77771, 77772, 77776-77778, 77781-77790, 77799, 0182T, C1325, C1348, C1350, C1700- C1712,

		C1715-C1720, C1728, C1790-C1806, C2616, C2632, C2633, C9120, C9216, C9430, C9714, C9715, G0174, G0178, G0179, G0251, G0256, G0261, G0273, G0274, G0338-G0340, J0128, J1675, J1950, J3315, J9165, J9202, J9217-J9219, J9225, J9226, Q2020, S0165, S0175, S0189, S9560
Pneumonitis	ICD-9	5088, 5089, 486, 5163, 5169
	ICD-10	J8411, J709, J708, J702, J703, J704, J189, J8489, J849
Hypothyroidism	ICD-9	2443, 2448, 2449
	ICD-10	E032, E038, E039
Diarrhea	ICD-9	787.91, 5645
	ICD-10	K591, K580, R197
Acute Kidney Injury	ICD-9	584.x
	ICD-10	N17.x
Emergency Room Visit	HCPCS/CPT	99281, 99282, 99283, 99284, 99285, 99291

MNSCLC: metastatic non-small cell lung cancer; ICI: immune checkpoint inhibitor; HCPCS: Healthcare Common procedure Coding System; ICD-9: International Classification of Diseases Nine Version; ICD-10: International Classification of Diseases Ten Version; NDC: National Drug Code

*These codes are used in washout cleaning but first-line treatment identification.

Supplementary Table 2. Patient characteristics from the emulated target trial of first-line ICI–Chemotherapy vs. ICI–Monotherapy for metastatic non–small cell lung cancer using SEER–Medicare data

Characteristic	ICI-Monotherapy[#]	ICI-Chemotherapy[#]
	N = 2,057	**N = 1,924**
Age[1] (Years)	78.0 (66.0, 91.0)	74.0 (66.0, 86.0)
Time from diagnosis to Treatment Initiations[1] (Days)	58.0 (22.0, 159.0)	55.0 (20.0, 137.9)
Charlson Comorbidity Index[1]	2.0 (0.0, 7.0)	2.0 (0.0, 7.0)
Immune Checkpoint Inhibitor		
Atezolizumab	17 (0.8%)	82 (4.3%)
Nivolumab	218 (10.6%)	12 (0.6%)
Pembrolizumab	1,822 (88.6%)	1,830 (95.1%)
Diagnosis Year		
2015, 2016	228 (11.1%)	-
2017	627 (30.5%)	>236 (12.3%)^
2018	636 (30.9%)	680 (35.3%)
2019	566 (27.5%)	997 (51.8%)
Geographic Region		
Midwest	140 (6.8%)	145 (7.5%)
Northeast	761 (37.0%)	637 (33.1%)
South	528 (25.7%)	631 (32.8%)
West	628 (30.5%)	511 (26.6%)
Metropolitan Status		
Metropolitan	1,781 (86.6%)	1,609 (83.6%)
Nonmetropolitan	276 (13.4%)	315 (16.4%)
Sex		

Female	1,046 (50.9%)	835 (43.4%)
Male	1,011 (49.1%)	1,089 (56.6%)
Race and Ethnicity		
Non-White	183 (8.9%)	208 (10.8%)
White	1,874 (91.1%)	1,716 (89.2%)
Radiation Therapy		
No	1,866 (90.7%)	1,761 (91.5%)
Yes	191 (9.3%)	163 (8.5%)
Yost index state quintiles (area level SES[2] deprivation)		
Unknown, blank	65 (3.2%)	54 (2.8%)
Group 1, lowest SES	183 (8.9%)	199 (10.3%)
Group 2, low-middle SES	336 (16.3%)	360 (18.7%)
Group 3, middle SES	461 (22.4%)	429 (22.3%)
Group 4, high-middle SES	490 (23.8%)	452 (23.5%)
Group 5, highest SES	522 (25.4%)	430 (22.3%)
Tumor Histology		
nonsquamous	1,617 (78.6%)	1,575 (81.9%)
squamous	440 (21.4%)	349 (18.1%)
Baseline Pneumonitis*		
No	1,391 (88.8%)	1,300 (88.9%)
Yes	175 (11.2%)	162 (11.1%)
Baseline Hypothyroidism*		
No	1,338 (85.4%)	1,278 (87.4%)
Yes	228 (14.6%)	184 (12.6%)
Baseline Diarrhea*		
No	1,529 (97.6%)	1,431 (97.9%)

Yes	37 (2.4%)	31 (2.1%)
Baseline Acute Kidney Injury*		
No	1,505 (96.1%)	1,412 (96.6%)
Yes	61 (3.9%)	50 (3.4%)
Baseline Emergency Room Visit*		
No	1,648 (80.1%)	1,571 (81.7%)
Yes	409 (19.9%)	353 (18.3%)
Chemotherapy		
Pemetrexed	-	37 (1.9%)
Carboplatin	-	67 (3.5%)
Carboplatin, Paclitaxel	-	426 (22.1%)
Carboplatin, Pemetrexed	-	1,362 (70.8%)
Others[3]	-	32 (1.7%)

#: Identification based on the first cycle (21 days) after first-line ICI initiation
*: Identification based on the 21 days before first-line ICI initiation (Index date)
–: Suppressed due to cell size < 11
^: Coarsened another category to suppress cells with size < 11 adequately
[1]Median with 2.5% lower bound and 97.5 % upper bound
[2]SES = socioeconomic status
[3]Others included Carboplatin; Carboplatin, Cisplatin, Docetaxel, Paclitaxel; Carboplatin, Docetaxel
Carboplatin, Gemcitabine; Carboplatin, Gemcitabine, Paclitaxel; Cisplatin, Pemetrexed; Docetaxel
Gemcitabine; Gemcitabine, Pemetrexed; Paclitaxel; Pemetrexed

Supplementary Table 3. Patient characteristics from the emulated target trial comparing 4-cycle vs. 6-cycle chemotherapy in the first-line ICI–Chemotherapy regimen for metastatic non–small cell lung cancer using SEER–Medicare data

Characteristic	4-cycle Chemotherapy[#]	6-Cycle Chemotherapy[#]
	N = 318	**N = 512**
Age[1] (Years)	74.0 (66.0, 87.0)	73.0 (66.0, 83.5)
Time from diagnosis to Treatment Initiations[1] (Days)	58.0 (21.0, 133.0)	57.0 (18.8, 144.0)
Baseline Charlson Comorbidity Index[1]	2.0 (0.0, 7.0)	2.0 (0.0, 7.0)
Immune Checkpoint Inhibitor		
Atezolizumab	17 (0.8%)	82 (4.3%)
Nivolumab	218 (10.6%)	12 (0.6%)
Pembrolizumab	1,822 (88.6%)	1,830 (95.1%)
Diagnosis Year		
2017	44 (13.8%)	68 (13.3%)
2018	108 (34.0%)	176 (34.4%)
2019	166 (52.2%)	268 (52.3%)
Geographic Region		
Midwest	31 (9.7%)	42 (8.2%)
Northeast	104 (32.7%)	205 (40.0%)
South	94 (29.6%)	148 (28.9%)
West	89 (28.0%)	117 (22.9%)
Metropolitan Status		
Metropolitan	254 (79.9%)	446 (87.1%)
Nonmetropolitan	64 (20.1%)	66 (12.9%)
Sex		
Female	182 (57.2%)	279 (54.5%)

Male	136 (42.8%)	233 (45.5%)
Race and Ethnicity		
Non-White	25 (7.9%)	61 (11.9%)
White	293 (92.1%)	451 (88.1%)
Radiation Therapy		
No	293 (92.1%)	482 (94.1%)
Yes	25 (7.9%)	30 (5.9%)
Yost index state quintiles (area level SES[2] deprivation)		
Unknown, blank	-	19 (3.7%)
Group 1, lowest SES	>31 (9.7%)^	44 (8.6%)
Group 2, low-middle SES	67 (21.1%)	86 (16.8%)
Group 3, middle SES	74 (23.3%)	121 (23.6%)
Group 4, high-middle SES	63 (19.8%)	126 (24.6%)
Group 5, highest SES	72 (22.6%)	116 (22.7%)
Tumor Histology		
nonsquamous	239 (75.2%)	450 (87.9%)
squamous	79 (24.8%)	62 (12.1%)
Baseline Pneumonitis*		
No	299 (94.0%)	502 (98.0%)
Yes	19 (6.0%)	-
Baseline Hypothyroidism*		
No	293 (92.1%)	471 (92.0%)
Yes	25 (7.9%)	41 (8.0%)
Baseline Diarrhea*		
No	>307 (96.5%)^	>501 (97.9%)^
Yes	-	-

Baseline Acute Kidney Injury*		
No	>307 (96.5%)^	>501 (97.9%)^
Yes	-	-
Baseline Emergency Room Visit*		
No	274 (86.2%)	485 (94.7%)
Yes	44 (13.8%)	27 (5.3%)
Immunotherapy Utilization*		
No	19 (6.0%)	27 (5.3%)
Yes	299 (94.0%)	485 (94.7%)

[#] Identification based on the fifth cycle (21 days) after 4-cycle of chemotherapy in ICI-Chemotherapy regimens

*Identification based on the 21 days before the fifth cycle of chemotherapy in the ICI-Chemotherapy regimen (Index date)

[1]Median with 2.5% lower bound and 97.5 % upper bound

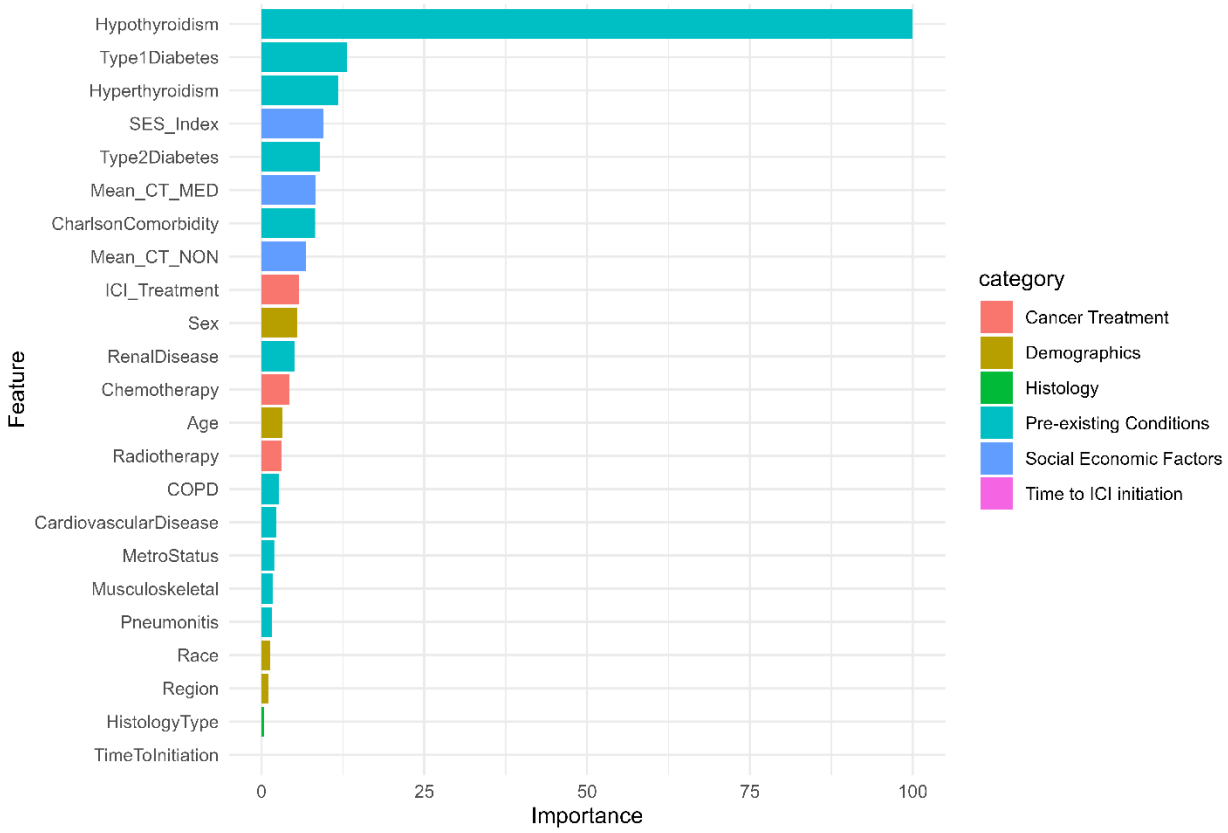
[2]SES = socioeconomic status

–: Suppressed due to cell size < 11

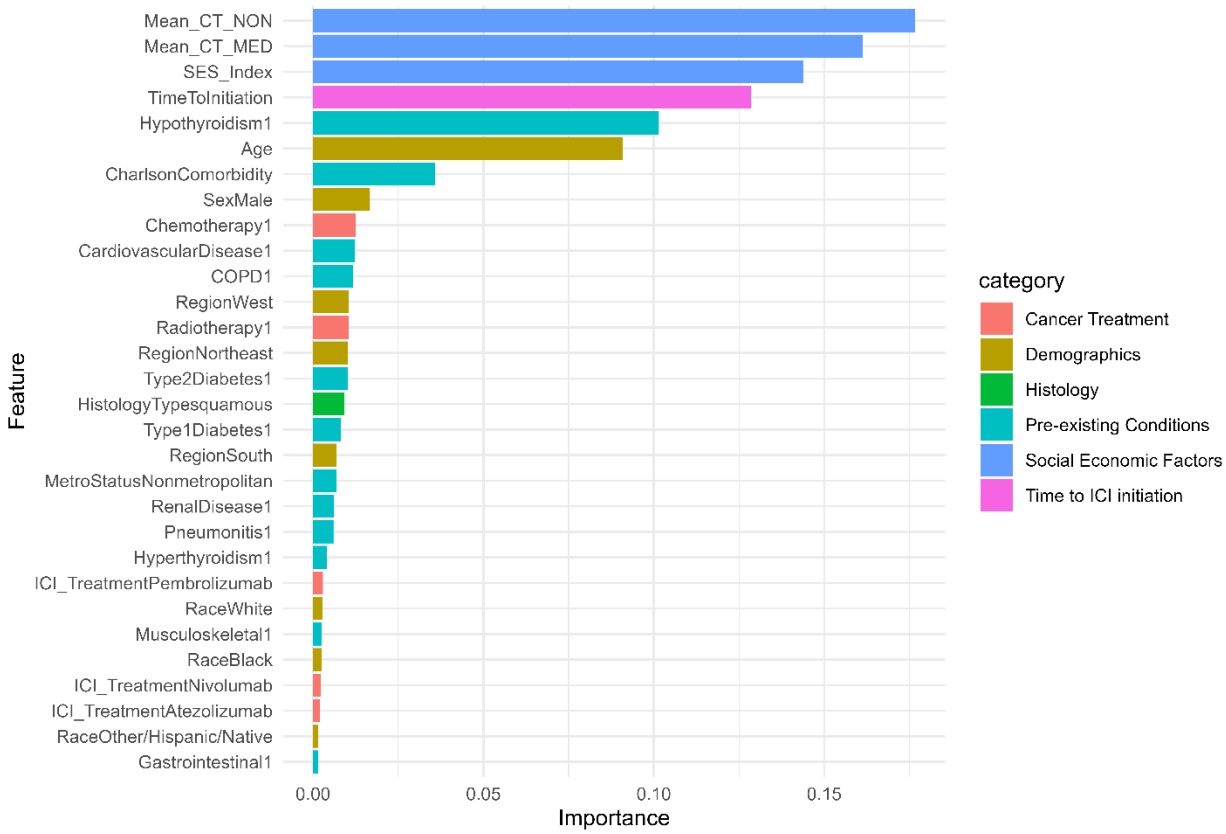
^: Coarsened another category to suppress cells with size < 11 adequately

Appendix for Aim 2 paper

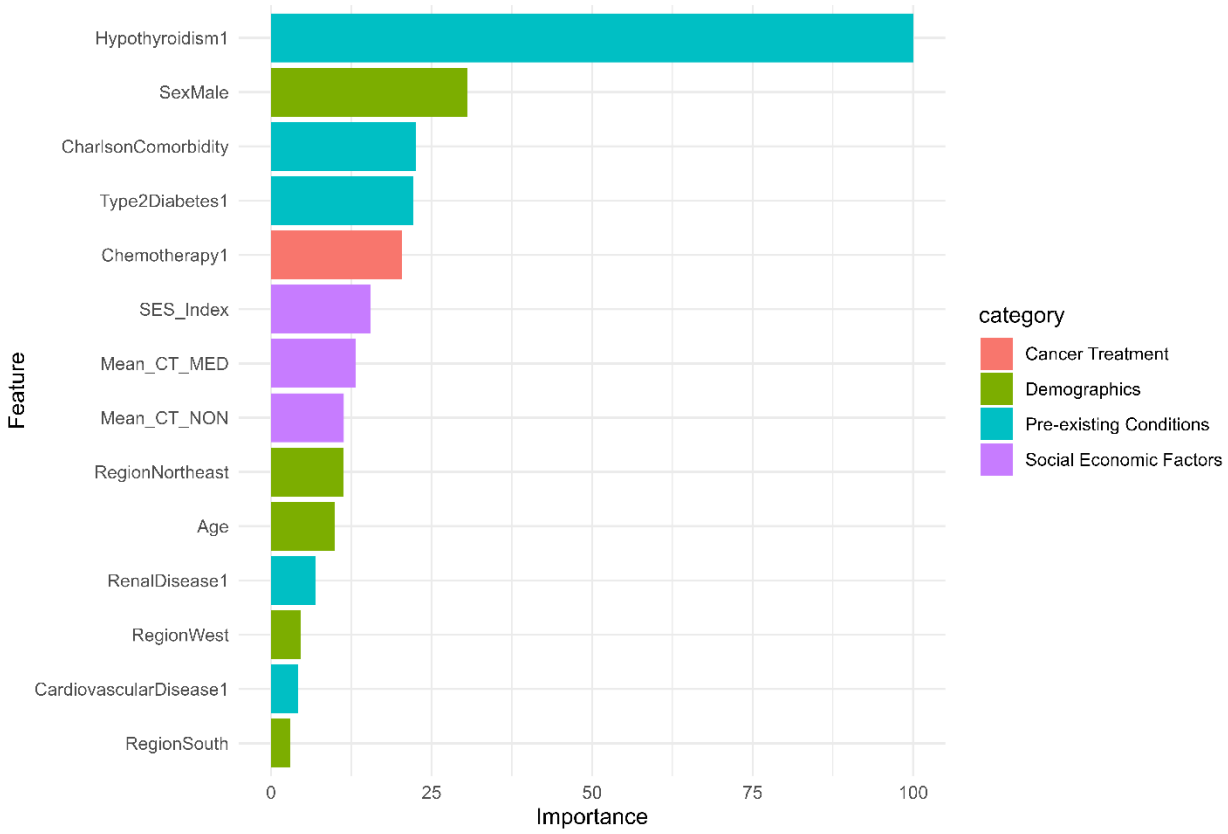
Supplementary Figure 1. Feature importance plot for Random Forrest in predicting the 3-month risk of endocrine-related irAEs



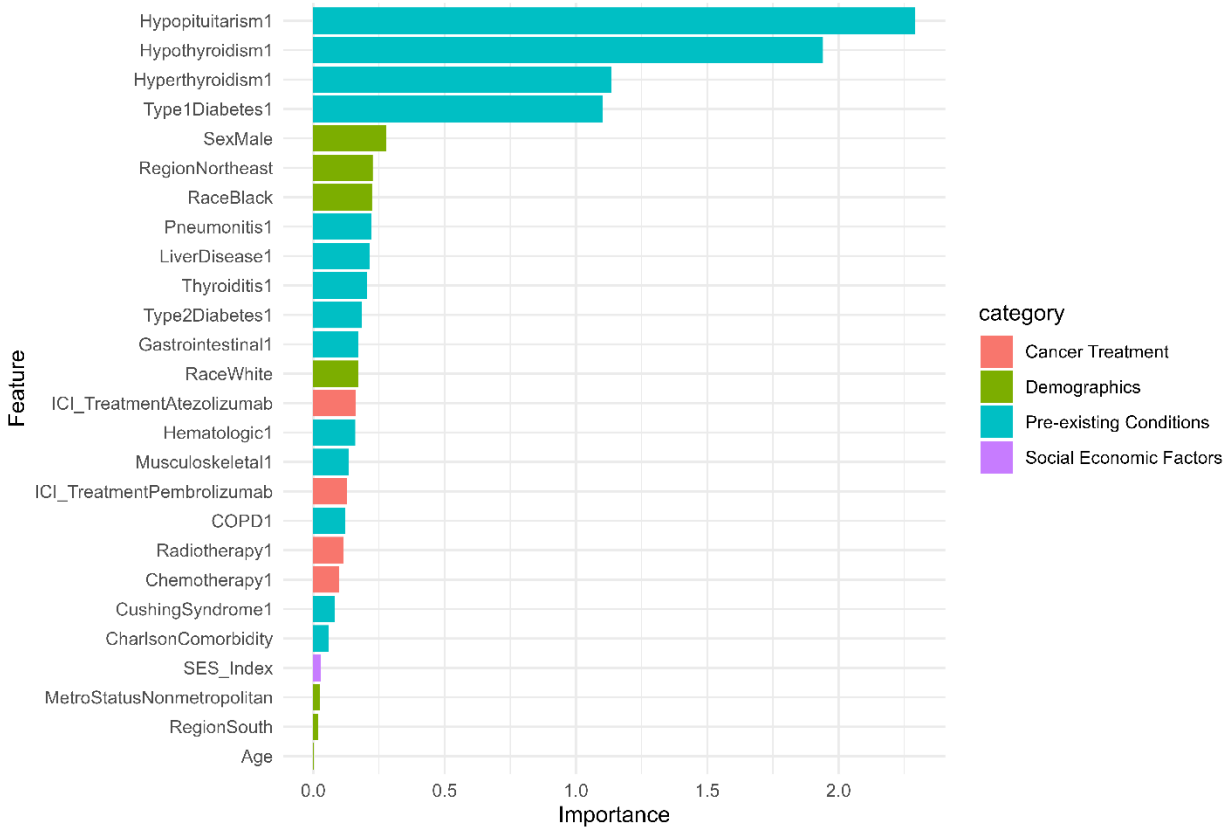
Supplementary Figure 2. Feature importance plot for XGboost in predicting the 3-month risk of endocrine-related irAEs



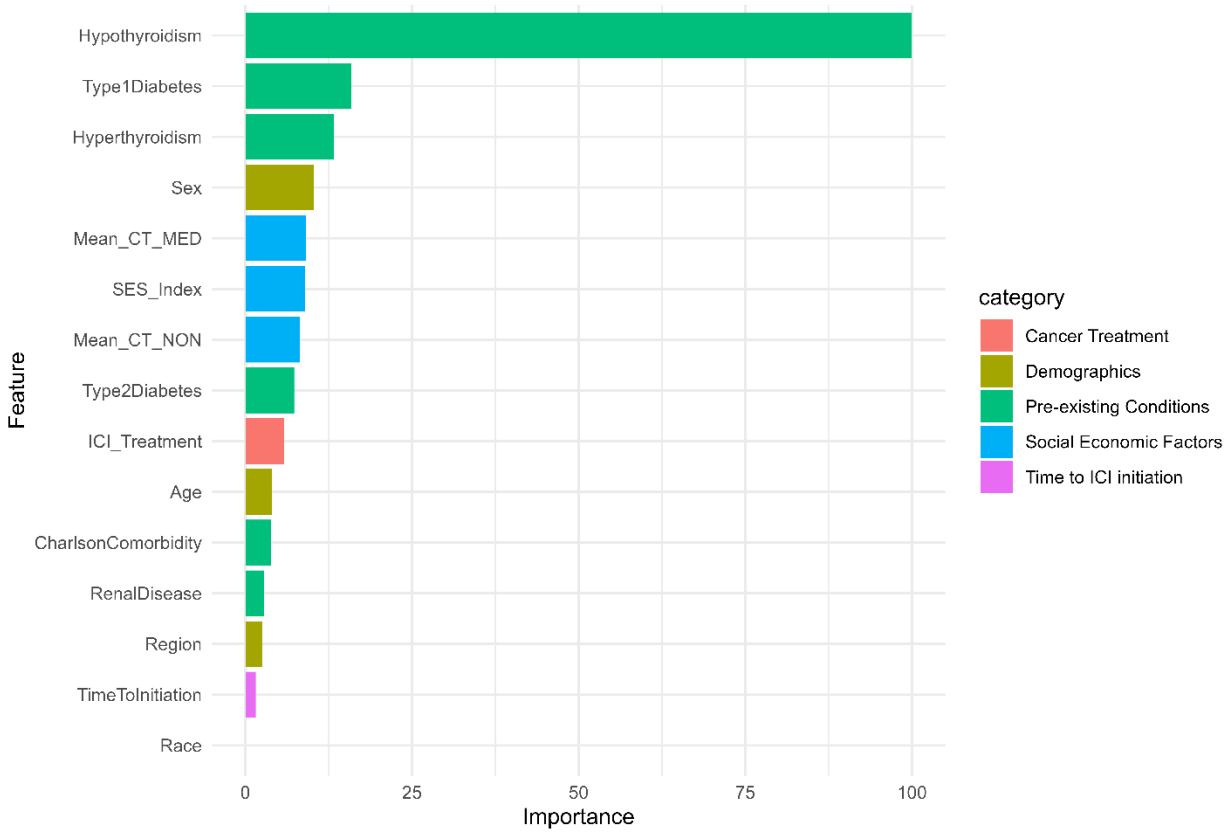
Supplementary Figure 3. Feature importance plot for SVM in predicting the 3-month risk of endocrine-related irAEs



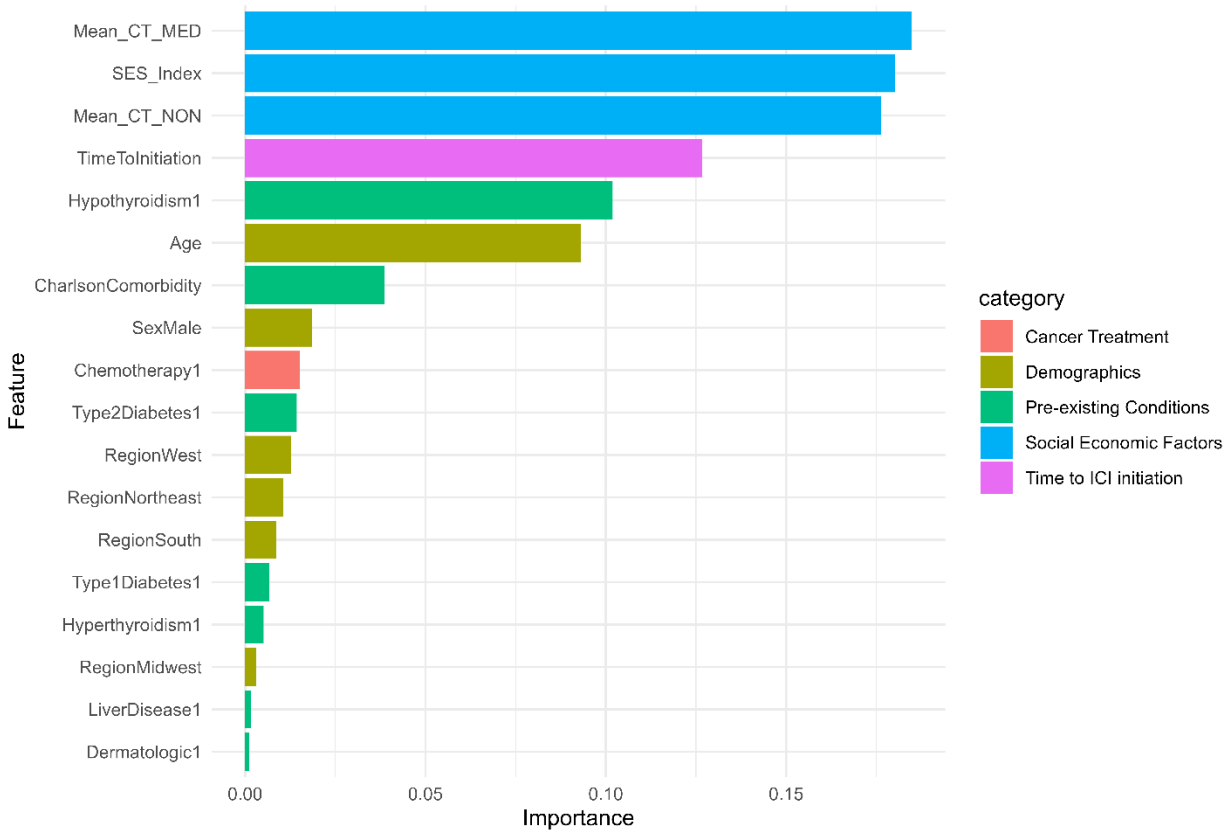
Supplementary Figure 4. Feature importance plot for LASSO in predicting the 6-month risk of endocrine-related irAEs



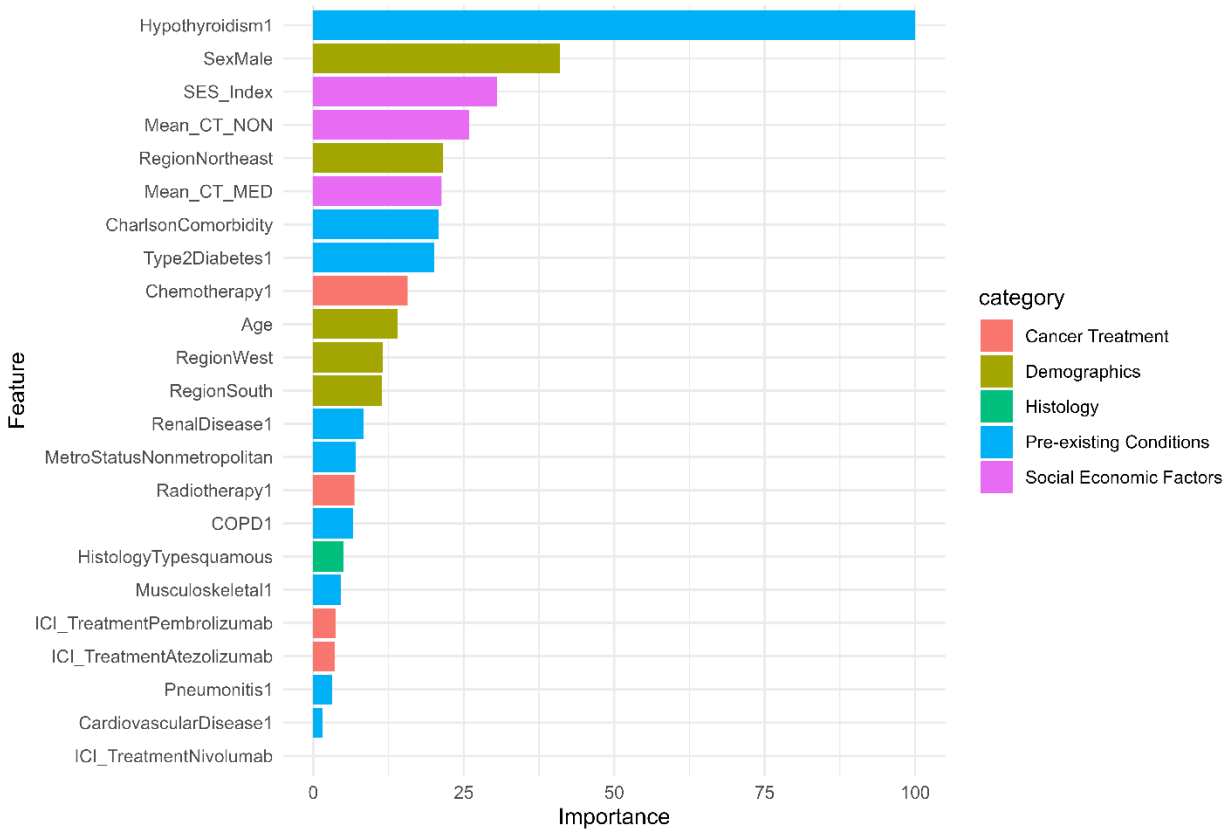
Supplementary Figure 5. Feature importance plot for Random Forrest in predicting the 6-month risk of endocrine-related irAEs



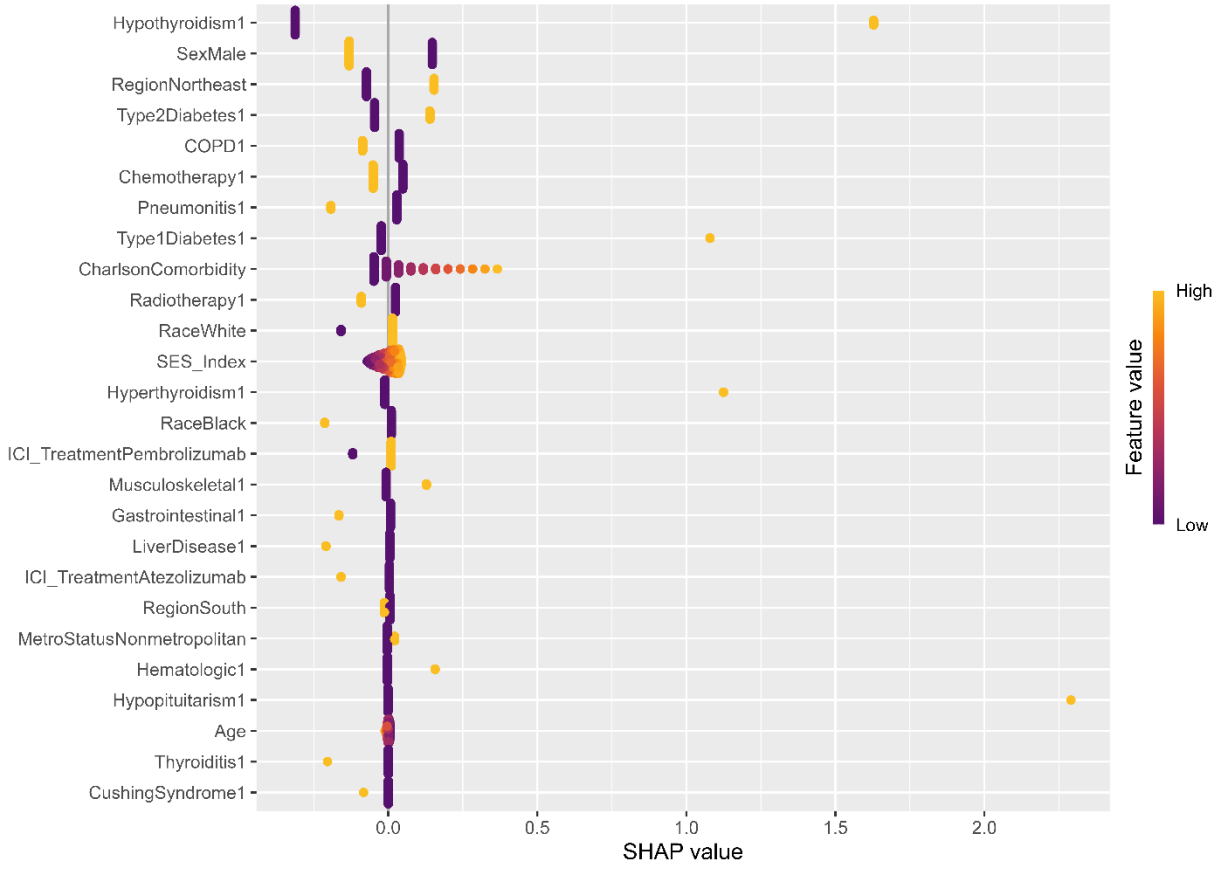
Supplementary Figure 6. Feature importance plot for XGboost in predicting the 6-month risk of endocrine-related irAEs



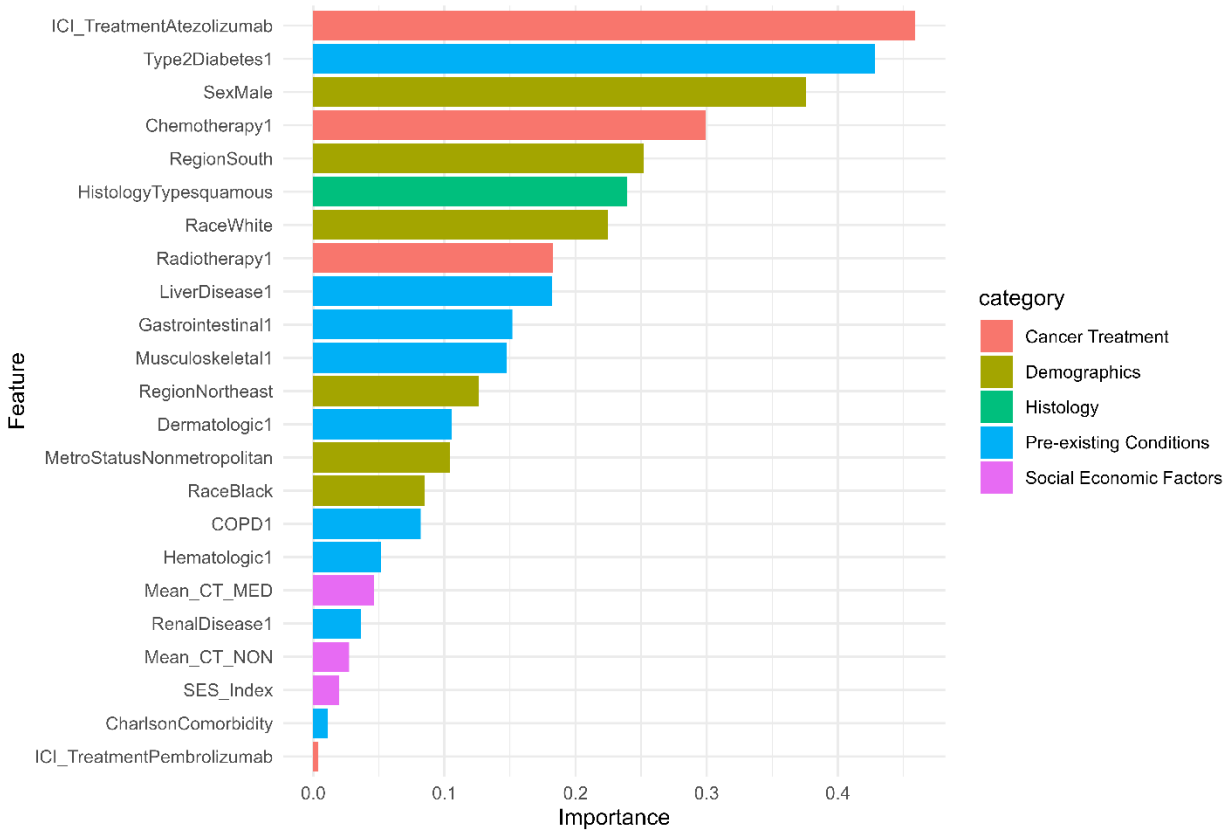
Supplementary Figure 7. Feature importance plot for SVM in predicting the 6-month risk of endocrine-related irAEs



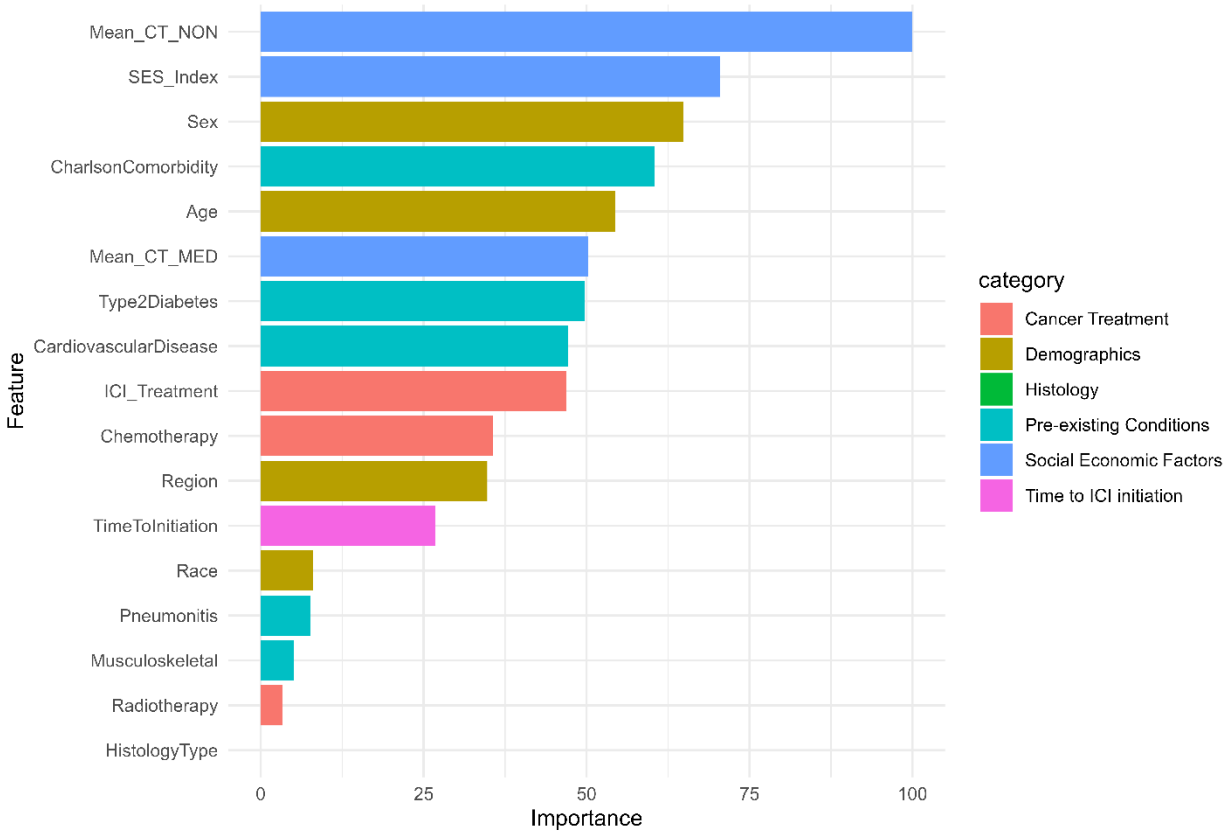
Supplementary Figure 8. SHAP value for LASSO in predicting the 6-month risk of endocrine-related irAEs



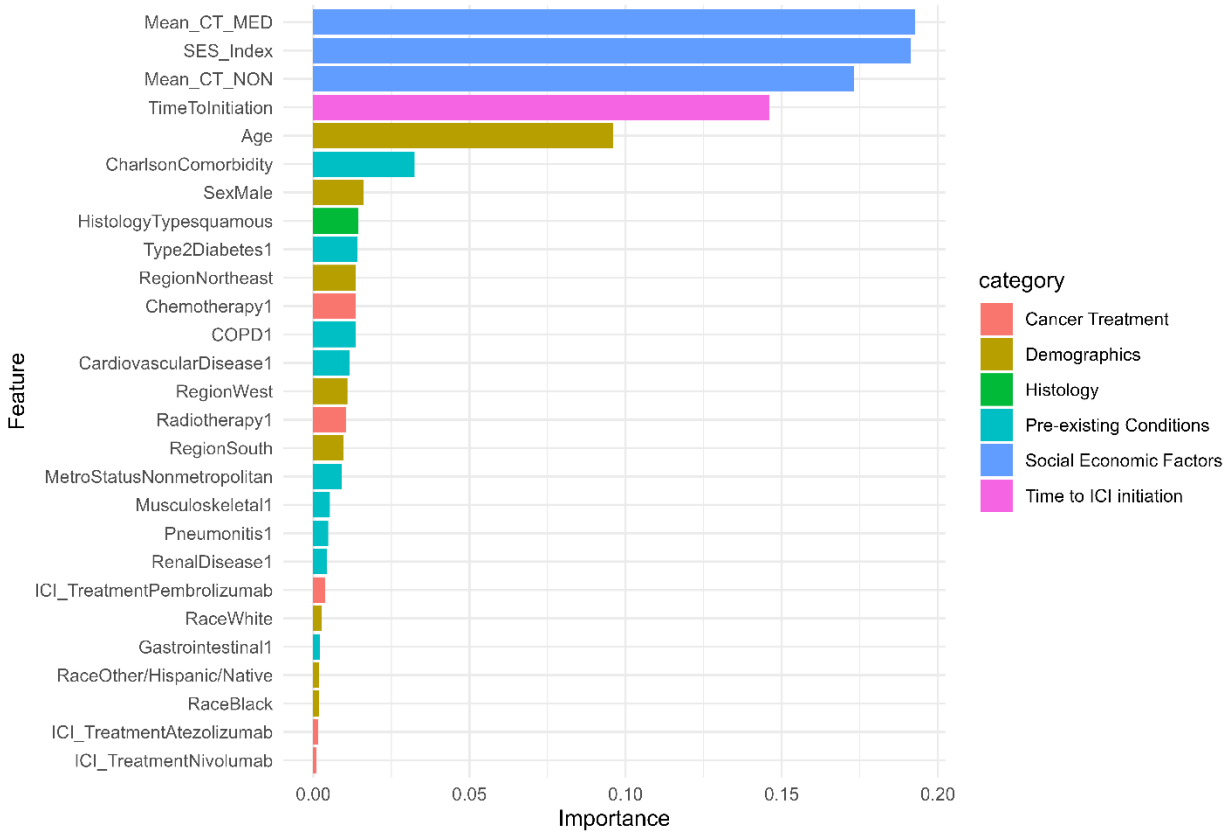
Supplementary Figure 9. Feature importance plot for LASSO in predicting the 3-month risk of endocrine-related irAEs in patients without pre-existing endocrine conditions



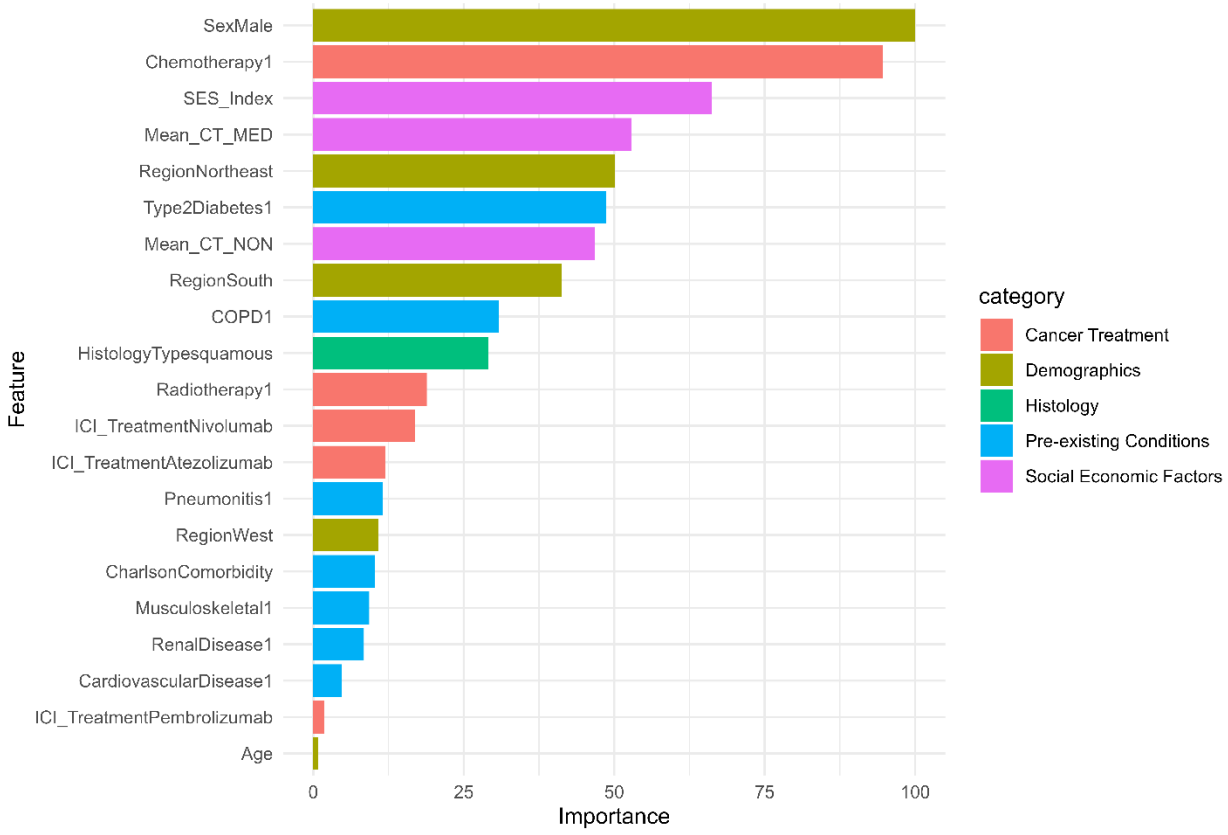
Supplementary Figure 10. Feature importance plot for Random Forrest in predicting the 3-month risk of endocrine-related irAEs in patients without pre-existing endocrine conditions



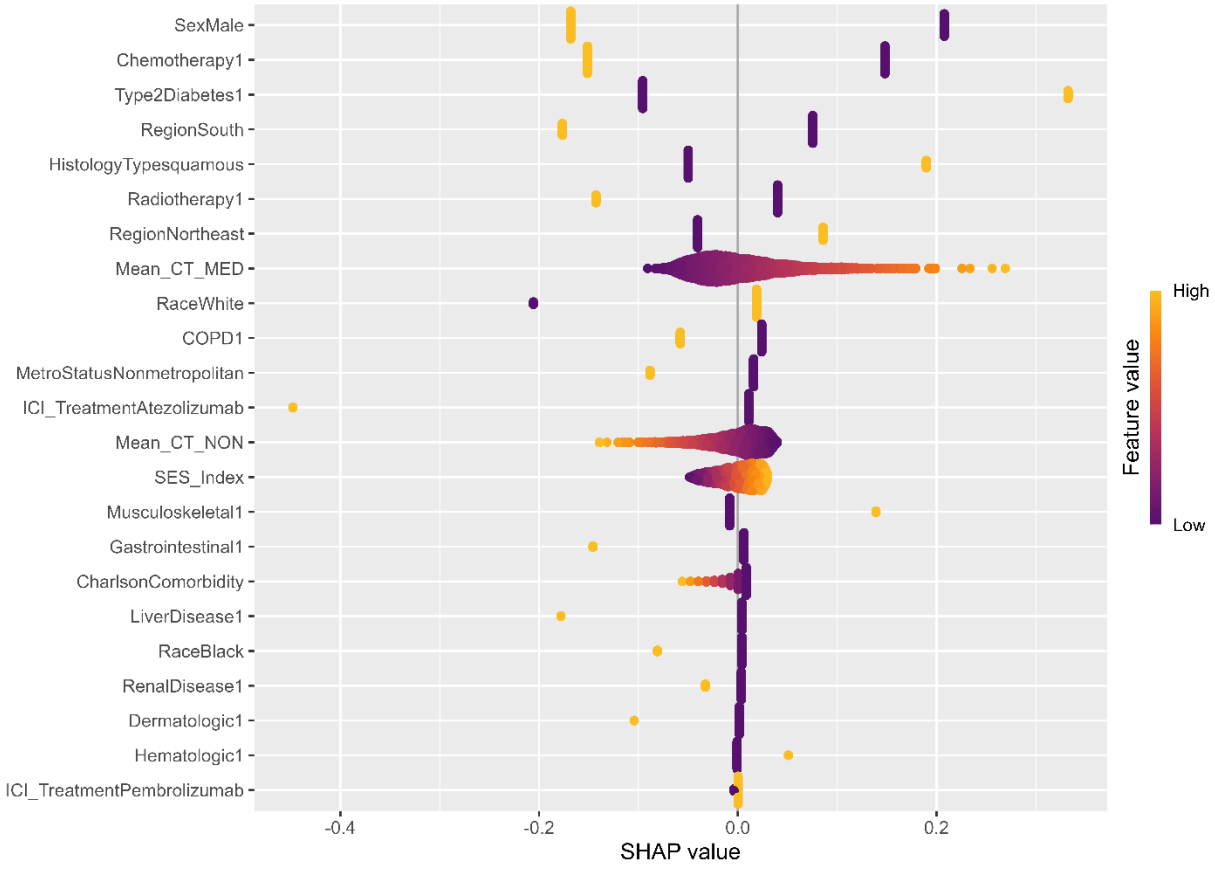
Supplementary Figure 11. Feature importance plot for XGboost in predicting the 3-month risk of endocrine-related irAEs in patients without pre-existing endocrine conditions



Supplementary Figure 12. Feature importance plot for SVM in predicting the 3-month risk of endocrine-related irAEs in patients without pre-existing endocrine conditions



Supplementary Figure 13. SHAP value for LASSO in predicting the 3-month risk of endocrine-related irAEs in patients without pre-existing endocrine conditions



Supplementary Table 1. ICD-O-3 codes for mNSCLC and medical codes for ICI, chemotherapy, and radiation treatment

Lung cancer ICD-O-3	C340-C343,C348-C349	
Histology ICD-O-3	Squamous	8010/3, 8012/3, 8020/3, 8046/3, 8050/3, 8051/3, 8140/3, 8141/3, 8143/3, 8147/3, 8250-8255/3, 8260/3, 8310/3,8430/3, 8480/3, 8481/3, 8490/3, 8560/3, and 8571-8575/3
	Non-squamous	8052/3, 8070-8083/3, 8570/3
ICI HCPCS	Atezolizumab	J9022, C9483
	Nivolumab	J9299, C9453
	Pembrolizumab	J9271, C9027
	Ipilimumab	J9228, C9284
	Durvalumab	J9173, C9492
	Cemiplimab	J9119
Chemotherapy ICD-9, ICD-10	ICD9	Diagnostic: V58.1, Procedure:99.25
	ICD10	Diagnostic: Z51.11, Procedure: 3E03305, 3E04305, XW03351, XW033B3, XW033C3, XW04351, XW043B3, XW043C3
Chemotherapy HCPCS	Carboplatin	J9045
	Cisplatin	C9418, J9060, J9062
	Docetaxel	J9170, J9171
	Paclitaxel	C9127, C9431, J9265, J9267, J9264
	Pemetrexed	C9213, J9304, J9305
	Gemcitabine	J9201, J9198
	Other HCPCS codes related to the chemotherapy*	96400, 96401, 96402, 96405, 96406, 96408, 96409, 96410, 96411, 96412, 96413, 96414, 96415, 96416, 96417, 96420, 96422, 96423, 96425, 96440, 96445, 96446, 96450, 96499, 96520, 96521, 96522, 96523, 96530, 96542, 96545, 96549, Q0083, Q0084, Q0085, Q2017, Q2024, S0087, S0088
Radiation	ICD-9codes	Diagnostic: V58.0, V66.1, V67.1, Procedure: 92.2, 92.20-92.29, 92.3, 92.30-92.33, 92.39, 92.4, 92.40, 92.41
	ICD-10 codes	Diagnostic: Z510, Procedure: 0HHT01Z, 0HHT31Z, 0HHT71Z, 0HHT81Z, 0HHTX1Z, 0HHU01Z, 0HHU31Z, 0HHU71Z, 0HHU81Z, 0HHUX1Z, 0HHV01Z, 0HHV31Z, 0HHV71Z, 0HHV81Z, 0HHVX1Z, 0HHW01Z, 0HHW31Z, 0HHW71Z, 0HHW81Z, 0HHWX1Z, 0HHX01Z, 0HHX31Z, 0HHX71Z, 0HHX81Z, 0HHXX1Z
	HCPCS	HCPCS/CPT: 76370, 76950, 76965, 77261-77263, 77280, 77285, 77290, 77293, 77295, 77299-77301, 77305-77307, 77310, 77315-77318, 77321, 77326-

		77328, 77331-77334, 77336, 77338, 77370-77373, 77385-77387, 77399, 77401-77404, 77406-77409, 77411-77414, 77416-77418, 77421-77425, 77427, 77431, 77432, 77435, 77469, 77470, 77499, 77520, 77522, 77523, 77525, 77750, 77761-77763, 77767, 77768, 77770, 77771, 77772, 77776-77778, 77781-77790, 77799, 0182T, C1325, C1348, C1350, C1700- C1712, C1715-C1720, C1728, C1790-C1806, C2616, C2632, C2633, C9120, C9216, C9430, C9714, C9715, G0174, G0178, G0179, G0251, G0256, G0261, G0273, G0274, G0338-G0340, J0128, J1675, J1950, J3315, J9165, J9202, J9217-J9219, J9225, J9226, Q2020, S0165, S0175, S0189, S9560

MNSCLC: metastatic non-small cell lung cancer; ICI: immune checkpoint inhibitor; HCPCS: Healthcare Common Procedure Coding System; ICD-9: International Classification of Diseases Nine Version; ICD-10: International Classification of Diseases Ten Version; NDC: National Drug Code

*These codes are used in washout cleaning but not first-line treatment identification.

Supplementary Table 2. ICD-9 and ICD-10 Codes for Endocrine irAEs and Pre-existing Conditions

Outcome			
Endocrine AEs	Hypothyroidism	244.3, 244.8, 244.9	E03.2, E03.8, E03.9
	Hyperthyroidism	242	E05.x
	Hypophysitis	253.8	E23.6
	Adrenal insufficiency	255.41	E27.1, E27.3, E27.4
	Diabetes Type I	250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93	E09.x, E10.x, E13
	Cushing's syndrome	255.0	E24.9, E24.0, E24.2
	Hypopituitarism	253.2, 253.7	E23.0, E23.1, E23.3
	Thyroiditis (acute thyroiditis, subacute thyroiditis, iatrogenic thyroiditis, thyroiditis unspecified)	245.1, 245.4, 245.9	E06.0, E06.1, E06.9
Pre-treatment conditions			
Endocrine*	Diabetes Type 2	250.x0, 250.x2	E11.x
Dermatologic	Eruption	693.0	L27.0, L27.1
	Pruritus	698.8	L29.8, L29.9
	Lichen planus	697.0	L43.x, L44.3, L66.1
	Vitiligo	709.00, 709.01, 709.09	L80, L81.8, L81.9
	Bullous Pemphigoid	694.5	L12.0
	Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN)	695.13, 695.14	L51.1, L51.3
Hematologic	Anemia	285.3, 285.8, 285.9, 284.x, 283.x	D59.x, D61.x, D60.x, D64.2, D64.3, D64.8

	Thrombocytopenia	287.3, 287.31, 287.8, 287.9, 287.31, 287.32, 287.4, 287.49, 287.5287.8, 287.9	D69.3, D69.41, D69.49, D69.59, D69.6
	Leukopenia	288.00, 288.03, 288.09 288.4, 288.5x, 288.8, 288.9	D72.1, D72.81, D72.810, D72.818, D72.819, D70.9, D70.4, D70.2, D76.1, D76.3
Pulmonary	Pneumonitis	508.8, 508.9, 486.x, 516.3x, 516.9	J84.11x, J70.9, J70.8, J70.2, J70.3, J70.4, J18.9, J84.89, J84.9
	Chronic Pulmonary Disease	416.8, 416.9, 506.4, 508.1, 508.8, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505	I27,8, I27,9, J68,4, J70,1, J70,3, J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67
Musculoskeletal	Dermatopolymyositis/ polymyositis	710.3, 710.4	M33
	Rheumatoid arthritis	714.x	M05, M06, M08.0, M08.2, M08.3, M08.4, M08.8, M08.9, M12.0
	Myalgia	729.1	M79.1
	Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA)	725, 446.5	M35.5, M31.5, M31.6
	Neuritis/neuralgia	729.2	M79.2
	Cardiac Arrhythmia	427.x	I48.x, I47.x, I49.x, I46.x
	Acute Myocardial Infarction	410.x	I21, I22
Cardiovascular	History of Myocardial Infarction	412	I252
	Myocarditis	422.x, 429.x	I40.x, I51.4, I51.8, I51.9
	Pericarditis	420.x, 423.x	I30.x, I31.4, I31.8-9
	Cardiomyopathy	425.4, 425.9	I42.0, I42.7, I42.9
	Congestive Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13,	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I43, I50, P29.0,

		404.91, 404.93, 428, 425.5, 425.6, 425.7, 425.8,	I42.5, I42.6, I42.7, I42.8, I42.9
	Peripheral Vascular Disease	093.0, 440, 441, 447.1, 557.1, 557.9, V43.4, 443.1, 443.2, 443.3, 443.4, 443.5, 443.6, 443.7, 443.8, 443.9	I70, I71, I73.1, I73.8, I73.9, I771, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
	Cerebrovascular Disease	362.34, 430, 431, 432, 433, 434, 435, 436, 437, 438	G45, G46, H340, I6
Renal	Chronic Kidney Disease and End-Stage Renal Disease	403,01, 403,11, 403,91, 404,02, 404,03, 404,12, 404,13, 404,92, 404,93, 582, 585, 586, 588,0, V420, V451, V56	I12,0, I13,1, N18, N19, N25,0, Z94,0, Z99,2
	Acute Kidney Injury	584.x	N17.x
	Acute Interstitial Nephritis	591.10, 591.11, 583.89	N10.x, N12.x, N14.1, N14.2
	Glomerulonephritis	580.x, 581.x	N00.x, N01.x, N04.x, N05.x, N06.x
Liver	Hepatitis	573.3, 790.5	K71, R74.8, K75.4, K75.9, R94.5
Gastrointestinal	Diarrhea	787.91, 564.5	K59.1, K58.0, R19.7
	Colitis	558.2, 558.3, 558.4, 558.9, 555, 556.8, 556.9	K52.1, K52.29, K52.3, K52.9, K52.89, K53.82
	Pancreatitis	577.0	K85.x
	Mucositis	528.x	K12.30, K12.31

IrAEs: Immune-related adverse events

Supplementary Table 3. Prediction performance for each machine learning model in predicting the 3-month risk of endocrine-related irAEs in patients without pre-existing endocrine conditions

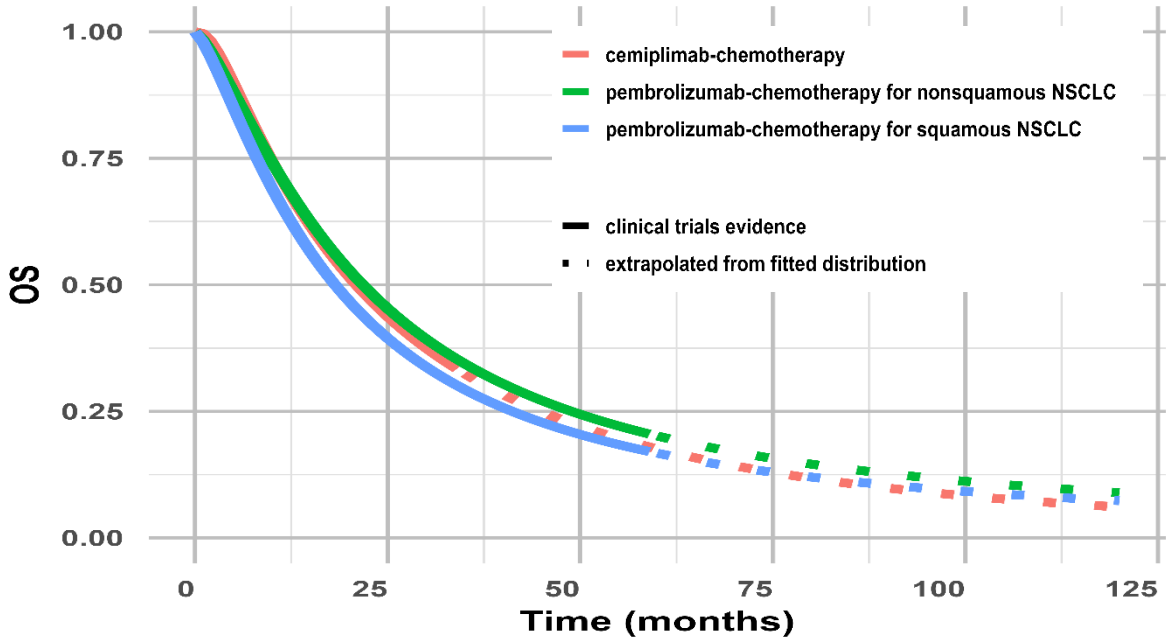
Model	Accuracy (95% CI)	F1 Score (95% CI)	AUROC (95% CI)
LASSO	0.7765 [0.7743, 0.7787]	0.1960 [0.1890, 0.2029]	0.5718 [0.5661, 0.5774]
RF	0.7734 [0.7715, 0.7752]	0.1756 [0.1690, 0.1822]	0.5401 [0.5348, 0.5454]
XGBoost	0.7659 [0.7643, 0.7674]	0.1411 [0.1353, 0.1468]	0.5244 [0.5196, 0.5292]
SVM	0.7710 [0.7693, 0.7727]	0.1599 [0.1537, 0.1661]	0.5174 [0.5102, 0.5245]

AUROC = Area under the receiver operating characteristic curve; CI = Confidence interval

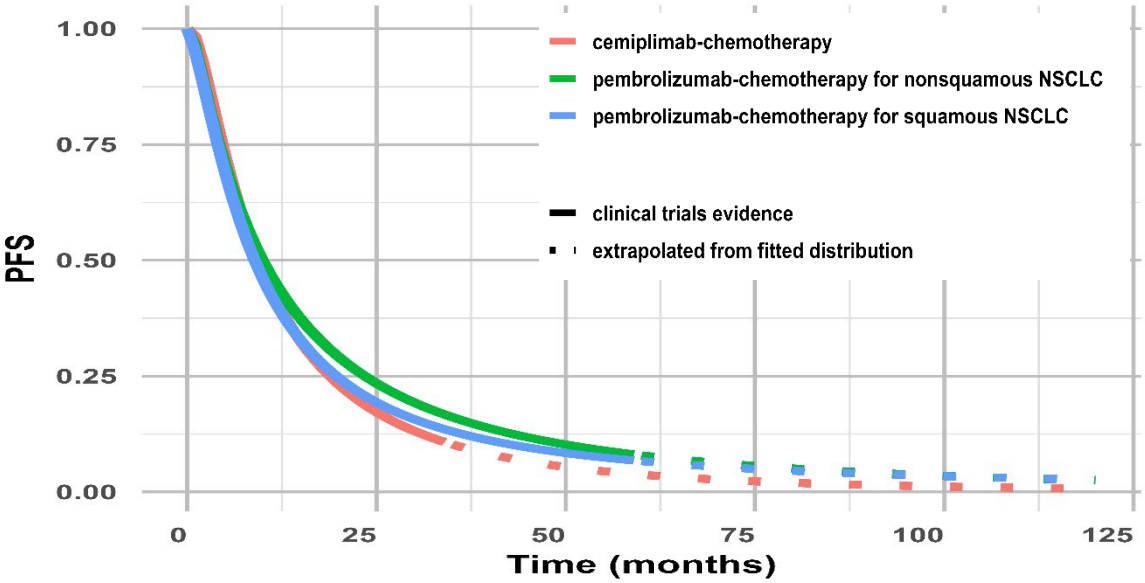
Appendix for Aim 3 paper

Supplementary Figure 1. Overall survival (A) and progression-free survival (B) curves derived from clinical trials

A.

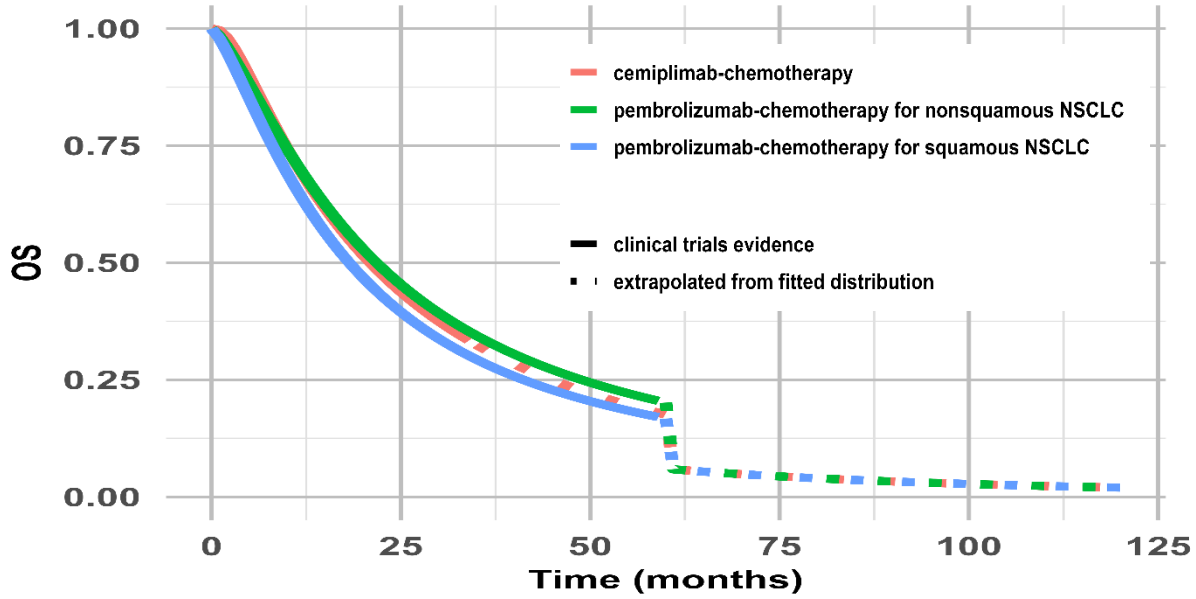


B.



OS: overall survival; PFS: progression-free survival

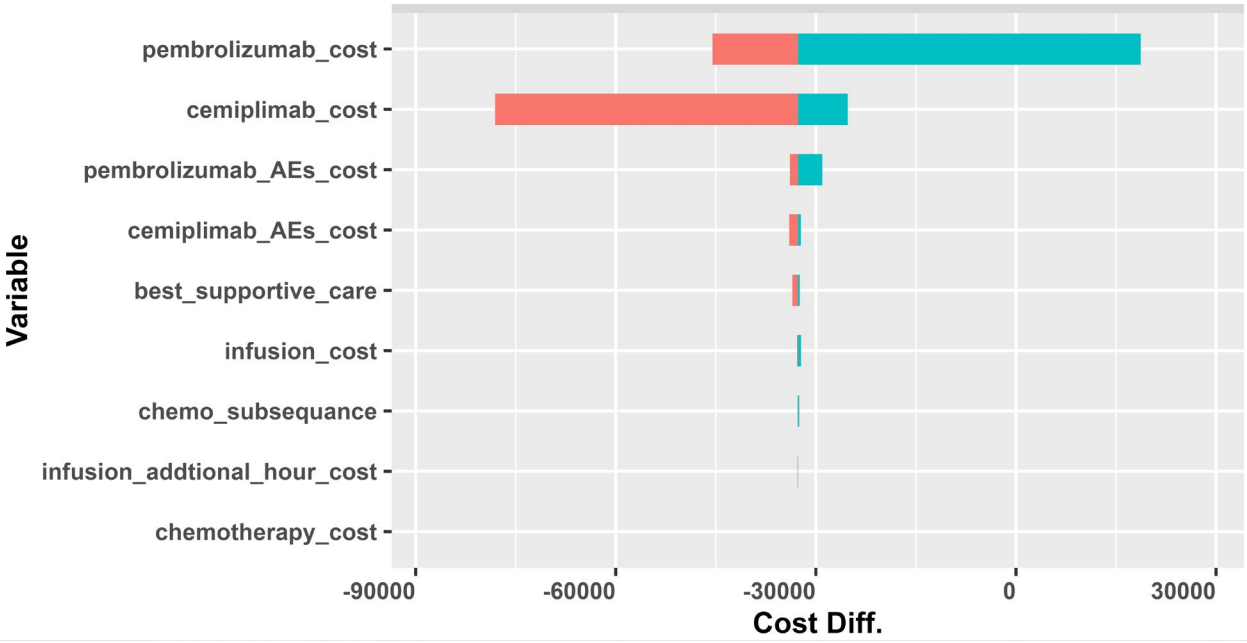
Supplementary Figure 2. Overall survival curves derived from clinical trials and SEER



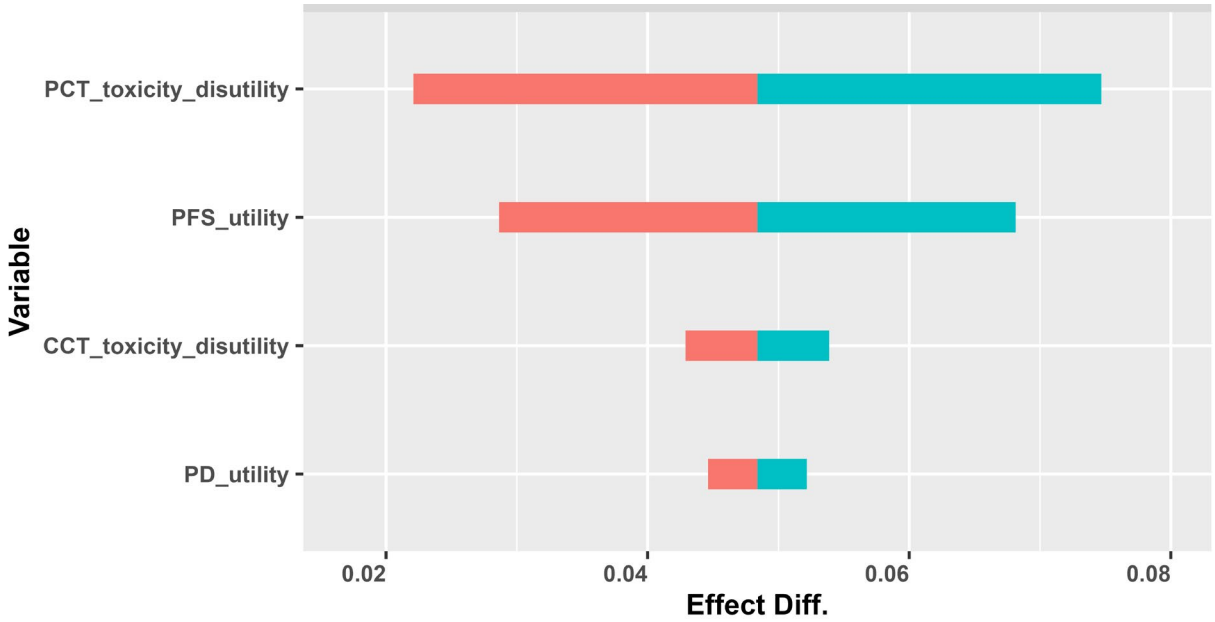
SEER: Surveillance, Epidemiology, and End Results
OS: Overall survival

Supplementary Figure 3. Tornado plot of base-case one-way sensitivity analysis of the cost (A) and QALYs (B) compared to pembrolizumab-chemotherapy

A.

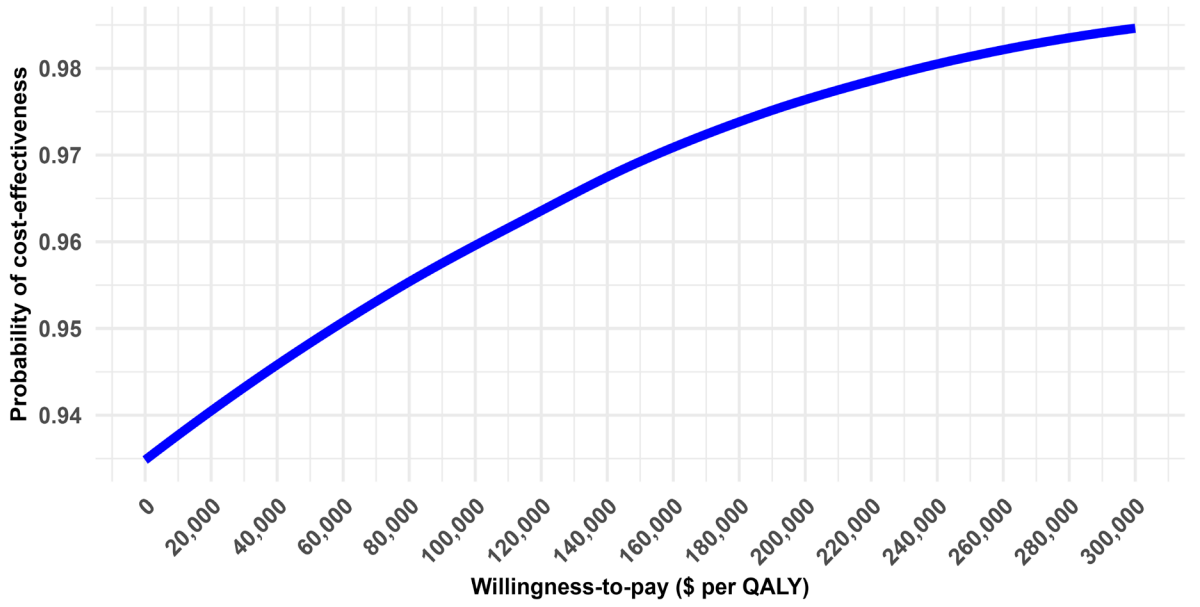


B.



QALY: quality-adjusted life year; PCT: pembrolizumab-chemotherapy; CCT: cemiplimab-chemotherapy; PFS: progression-free survival ; PD: progressed disease

Supplementary Figure 4. Cost-effectiveness acceptability curve of cemiplimab-chemotherapy



Supplementary Table 1. Comparison of fitness of parametric survival models

Treatment	Model	OS_AIC	OS_BIC	PFS_AIC	PFS_BIC
cemiplimab-chemotherapy	Exponential	2,814.46	2,818.48	1,719.68	1,723.42
	Weibull	2,813.57	2,821.60	1,717.54	1,725.02
	Gamma	2,816.41	2,824.44	1,712.33	1,719.82
	Log-Normal	2,759.63	2,767.66	1,676.55	1,684.03
	Gompertz	2,790.67	2,798.71	1,720.68	1,728.17
	Log-Logistic	2,762.46	2,770.49	1,686.59	1,694.08
pembrolizumab-chemotherapy for squamous patients	Exponential	1,986.43	1,990.06	1,859.89	2,818.48
	Weibull	1,986.98	1,994.24	1,849.11	2,821.60
	Gamma	1,988.26	1,995.51	1,857.66	2,824.44
	Log-Normal	1,970.83	1,978.09	1,798.35	2,767.66
	Gompertz	1,975.06	1,982.31	1,807.59	2,798.71
	Log-Logistic	1,965.11	1,972.37	1,792.82	2,770.49
pembrolizumab-chemotherapy for nonsquamous patients	Exponential	2,946.09	2,950.11	2,814.46	2,818.48
	Weibull	2,948.09	2,956.12	2,813.57	2,821.60
	Gamma	2,947.94	2,955.97	2,816.41	2,824.44
	Log-Normal	2,957.10	2,965.13	2,759.63	2,767.66
	Gompertz	2,944.65	2,952.69	2,790.67	2,798.71
	Log-Logistic	2,938.91	2,946.94	2,762.46	2,770.49

AIC: Akaike information criterion; BIC: Bayesian Information Criterion; OS: Overall survival; PFS: Progression-free survival.

Supplementary Table 2. Associated costs and disutility of grade ≥ 3 treatment-related adverse events

Adverse Event [a]	Probability	Disutility	Reference	Cost in 2024 USD [b]	Reference
Cemiplimab-chemotherapy					
Anemia	0.109	-0.073	Paul et al. [1]	26617.96	Wong et al. [2]
Neutropenia	0.064	-0.350	Nafees et al. [3]	22572.71	Wong et al. [2]
Pembrolizumab-chemotherapy (Nonsquamous)					
Anemia	0.190	-0.073	Paul et al. [1]	26617.96	Wong et al. [2]
Diarrhea	0.052	-0.220	Nafees et al. [3]	21691.14	Insinga et al. [4]
Asthenia	0.067	-0.290	Nafees et al. [3]	1216.84	Wong et al. [2]
Thrombocytopenia	0.086	-0.108	Konidaris et al. [5]	29821.05	Wong et al. [2]
Neutropenia	0.168	-0.350	Nafees et al. [3]	22572.71	Wong et al. [2]
Pembrolizumab-chemotherapy (Squamous)					
Anemia	0.158	-0.073	Paul et al. [1]	26617.96	Wong et al. [2]
Thrombocytopenia	0.083	-0.108	Konidaris et al. [5]	29821.05	Wong et al. [2]
Neutropenia	0.230	-0.350	Nafees et al. [3]	22572.71	Wong et al. [2]
Weighted Average [c]					
Cemiplimab-chemotherapy		0.030		4346.01	
Pembrolizumab-chemotherapy [d]		0.127		12194.16	

a: Treatment-related adverse events grade ≥3 and more than 0.05 incidence in clinical trial
b: Cost are adjusted to 2024 USD based on US Consumer Price Index
c: Calculated as an average cost and disutility of toxicity using the weighted probability of occurrence.
d: Squamous and non-squamous NSCLC are weighted as 0.429 and 0.571 (same histology distribution in EMPOWER-Lung 3 trial)

Supplementary Table 3. Network meta-analysis results

Trial	Patients	Treatment	OS HR [a]	OS NMA [a]	PFS HR [a]	PFS NMA [a]
All patients						
EMPOWER-Lung 3[6]	squamous/nonsquamous aNSCLC	CCT vs. chemotherapy	0.65 (0.51,0.82)	1.0041 (0.73, 1.39)	0.55 (0.44,0.68)	1.01 (0.69, 1.49)
KEYNOTE-407[7]	squamous aNSCLC	PCT vs. chemotherapy	0.71 (0.59,0,85)		0.62 (0.52,0.74)	
KEYNOTE-189[8]	nonsquamous aNSCLC	PCT vs. chemotherapy	0.60 (0.50, 0.72)		0.50 (0.42,0.60)	
PD-L1≥50%						
EMPOWER-Lung 3[6]	squamous/nonsquamous aNSCLC	CCT vs. chemotherapy	0.56 (0.36,0.86)	1.21 (0.74, 2.00)	0.48 (0.32,0.72)	0.85 (0.48, 1.50)
KEYNOTE-407[7]	squamous aNSCLC	PCT vs. chemotherapy	0.68 (0.47, 0.97)		0.48 (0.33, 0.69)	
KEYNOTE-189[8]	nonsquamous aNSCLC	PCT vs. chemotherapy	0.68 (0.49,0.96)		0.35 (0.25,0.49)	
PD-L1 1%-49%						
EMPOWER-Lung 3[6]	squamous/nonsquamous aNSCLC	CCT vs. chemotherapy	0.50 (0.34,0.74)	1.26 (0.80, 1.96)	0.48 (0.34,0.68)	1.22 (0.81, 1.84)
KEYNOTE-407[7]	squamous aNSCLC	PCT vs. chemotherapy	0.61 (0.45,0,83)		0.60 (0.45,0,81)	
KEYNOTE-189[8]	nonsquamous aNSCLC	PCT vs. chemotherapy	0.65 (0.46, 0.90)		0.57 (0.41, 0.80)	
PD-L1<1%						
EMPOWER-Lung 3[6]	squamous/nonsquamous aNSCLC	CCT vs. chemotherapy	0.94 (0.62,1.42)	0.72 (0.34, 1.52)	0.73 (0.50,1.08)	0.94 (0.60, 1.46)
KEYNOTE-407[7]	squamous aNSCLC	PCT vs. chemotherapy	0.83 (0.61, 1.13)		0.70 (0.52,0.95)	
KEYNOTE-189[8]	nonsquamous aNSCLC	PCT vs. chemotherapy	0.55 (0.39,0,76)		0.67 (0.49,0.92)	

OS: overall survival, HR: hazard ratio, NMA: network meta-analysis, PCT: pembrolizumab-chemotherapy, CCT: cemiplimab-chemotherapy, a: 95% confidence interval was reported

Supplementary Table 4. Results from subgroup analyses

	Treatment	Total cost ($)	Total QALYs	Incremental cost ($)	Incremental QALY	ICER ($/QALY)
PD-L1≥50%	PCT	210,163	1.537	—	—	—
	CCT	175,247	1.657	-34,916	0.119	-291,569
PD-L1 1%-49%	PCT	188,617	1.194	—	—	—
	CCT	175,247	1.657	-13,370	0.463	-28,900
PD-L1<1%	PCT	228,774	1.749	—	—	—
	CCT	175,247	1.657	-53,527	-0.092	578,974

PD-L1: programmed cell death ligand 1
PCT: pembrolizumab-chemotherapy
CCT: cemiplimab-chemotherapy
QALY: quality-adjusted life-year
ICER: incremental cost-effectiveness ratio

Reference for Aim 3 paper appendix:

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