Original Article

Clinical and financial impact of immune checkpoint inhibitors following platinum chemotherapy in patients with advanced or metastatic non-small cell lung cancer: a nationwide population-based study

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Background: Although various studies have demonstrated that the clinical efficacy of immune checkpoint inhibitors (ICIs) improves the prognosis of patients with non-small cell lung cancer (NSCLC), studies on the financial aspects based on large population-based data are needed. This study aimed to analyze the differences in medical expenses and the effect of ICIs on the prognosis of patients with advanced or metastatic NSCLC.

Methods: Patients newly diagnosed with stage IIIB or IV NSCLC who received palliative chemotherapy between 2013 and 2020 were selected from the nationwide database of the population covered by the Korean National Health Insurance Service. Interrupted time-series analysis was performed to evaluate the effects of subsequent ICI use after platinum-based cytotoxic chemotherapy (CC) on overall mortality. Progression-free survival and medical expenditure were also assessed.

Results: In the final study population, 2,485 and 4,812 patients were included in the ICI and non-ICI groups, respectively. ICI treatment significantly lowered the risk of death [adjusted hazard ratio, 0.79; 95% confidence interval (CI): 0.75–0.84]. And the ICI-treated patients were less likely to experience disease progression (adjusted odds ratios, 0.92; 95% CI: 0.85–0.99). Furthermore, after the introduction of ICIs, both total and cancer-related medical expenses per capita showed an increasing trend [β: $4.56K, standard error (SE): $0.27K, P<0.0001 and β: $4.54K, SE: $0.27K, P<0.0001, respectively].

Conclusions: Subsequent ICI use after platinum-based CC improved the overall survival rate of patients with advanced NSCLC. With the increasing burden of individual medical expenses, further research is required to identify patients for whom ICI treatment may be effective.

Keywords: Non-small cell lung cancer (NSCLC); immune checkpoint inhibitor (ICI); pembrolizumab; nivolumab; mortality

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Introduction

Background

Lung cancer is the most common carcinoma worldwide in terms of the morbidity and mortality associated with it (1,2). According to the Korea Cancer Registry, lung cancer has the third highest incidence among all carcinomas and is the most common cause of cancer-related death in the country (3,4). The crude incidence rate of lung cancer is increasing among both men and women every year, and it is expected to increase further after the introduction of the national lung cancer screening project in July 2018 (5).

Since the 2000s, research advances in biomarkers, such as *EGFR*, *ALK*, *RET*, *BRAF*, *ROS1*, *NTRK*, *MET*, and *KRAS*, to select patients for targeted and immunotherapy-based treatment have changed the treatment paradigm for non-small cell lung cancer (NSCLC) (6-8). Nevertheless, platinum-based chemotherapy regimens have been the mainstay treatments for most patients with NSCLC for whom an identifiable targeted therapy (TT) is not a treatment option. For decades, the median overall survival (OS) for advanced or metastatic disease has been less than 2 years (9,10).

The development of immune checkpoint inhibitors (ICIs) has dramatically changed the landscape of lung cancer treatment, demonstrating OS benefit (11,12). After ICIs were shown to improve OS and progression-free survival (PFS) when administered as second- and subsequent lines of treatment compared with chemotherapy, the US Food and Drug Administration approved nivolumab and pembrolizumab in 2015, the first two monoclonal antibodies targeting programmed cell death protein 1 (PD-1), for patients with advanced NSCLC (13-16). In the Republic of Korea, ICIs have been available as a second-line treatment for patients with advanced and metastatic lung cancer since July 2016.

Rationale and knowledge gap

Although various studies have demonstrated that the clinical efficacy of ICIs contributes to improving the prognosis of patients with NSCLC, more studies on the financial aspects based on large population-based data are needed (17-19).

Objective

This study aimed to analyze the differences in medical expenses and the effect of ICIs on prognosis improvement in patients with advanced or metastatic NSCLC. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-686/rc).

Highlight box

Key findings

- Immune checkpoint inhibitors (ICI) treatment led to longer survival and better prognosis in terms of overall survival and progression-free survival compared with cytotoxic chemotherapy (CC). However, the retention rate of ICIs was lower than targeted therapy (TT). Additionally, with ICI treatment, the increase in medical expenses for lung cancer treatment was higher than that with TT.

What is known and what is new?

- The survival benefit of subsequent ICI use after platinum-based CC is well established in patients with advanced non-small cell lung cancer.
- Our study found changes in the patterns of chemotherapy drug prescriptions after the coverage expanded, with a significant increase in annual medical expenses per patient.

What is the implication, and what should change now?

- Considering that a significantly higher medical cost was observed after ICI therapy, extensive profiling of TTs and ICIs is essential to improve the selection and sequencing of treatments, reduce the likelihood of ineffective therapies, and enhance patient outcomes.

Methods

Data source and study design

All Korean residents are enrolled in the Korean National Health Insurance Service (NHIS) and given a unique identification number at birth. Data accompany claims on fully adjudicated medical and pharmacy claims in the Republic of Korea, including general demographic data, the 10th revision of the International Statistical Classification

of Diseases (ICD-10) and Related Health Problems codes, medical institution type, medications prescribed, medical cost, and mortality. This retrospective cohort study evaluated nationwide data from the Korean NHIS. All outpatients and hospitalized patients with lung cancer between 2010 and 2020 were identified.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Institutional Review Board of the NHIS Ilsan Hospital (NHIMC 2022-10-015). Individual consent for this retrospective analysis was waived.

Case identification

A flowchart of the identification of the study population is shown in *Figure 1*. Among the 346,505 patients with lung cancer who were initially screened, 102,964 assigned diagnostic codes for lung cancer (C34) before 2013 were excluded. Patients without a history of cancer-related diagnostic procedures or chemotherapeutic treatment and those with cancer diagnostic codes other than that for lung cancer were excluded. The billing codes used for the diagnosis were biopsy methods using fiberoptic bronchoscopy and computed tomography-guided needle aspiration. The treatment billing codes consisted of lung surgery and radiotherapy (body or brain), and the prescribed drugs were paclitaxel, pemetrexed, gemcitabine, docetaxel, erlotinib, afatinib, ceritinib, crizotinib, gefitinib, pembrolizumab, and nivolumab. The remaining 139,783 patients were selected as patients newly diagnosed with NSCLC between January 1, 2013, and December 31, 2020.

Patients who underwent lung surgery were considered as having early-stage NSCLC; those who received concurrent chemoradiation therapy as having locally advanced NSCLC; and those who received only systemic cytotoxic chemotherapy (CC), TT, or ICI appropriate for NSCLC as having metastatic or recurrent disease. Therefore, to identify patients with stage IIIB or IV NSCLC, the following operational definitions were used: (I) first-ever administration of TTs such as afatinib, ceritinib, crizotinib, erlotinib, or gefitinib; (II) use of CC such as paclitaxel, pemetrexed, gemcitabine, docetaxel, irinotecan, or etoposide administered at least 180 days after radiation therapy or resection surgery of the lung parenchyma; (III) first-ever administration of CC without a history of radiation therapy or resection surgery of the lung parenchyma; (IV) conditions (I), (II), and (III) were started after January 1, 2013; and (V) the observation duration was at least 6 months long. Overall, 49,842 patients were found to have been diagnosed with stage IIIB or IV NSCLC and received palliative chemotherapy.

To evaluate the effect of ICIs as second-line chemotherapeutics, patients who met the following criteria were further screened as patients treated with second-line chemotherapeutics: (I) initial chemotherapy started after January 2016, (II) ICI was not administered as first-line chemotherapy, (III) TT was not administered as first-line chemotherapy, (IV) history of second-line chemotherapy, (V) ICIs were not administered as third (or higher)-line chemotherapy and (VI) atezolizumab was not administered. A total of 7,297 patients who were diagnosed with stage IIIB or IV NSCLC and received second-line chemotherapy were included in the final study population. Among them, 2,485 and 4,812 patients were divided into groups depending on their history of ICI administration as second-line chemotherapeutics.

Charlson comorbidity index (CCI)

The CCI is a widely used prognostic model that predicts the 1-year mortality risk, depending on individual comorbidities. Each comorbidity was scored, and the CCI was calculated by summing the comorbidity scores (Table S1). Because of its usefulness in measuring the effects of comorbidities on mortality by using an administrative database, including ICD-10 codes, the CCI was adopted as a variable (20,21).

Covariates

Age, sex, income level, type of hospital, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), congestive heart failure (CHF), cerebrovascular disease, stage, and brain metastasis were used as adjustment variables. Additionally, sensitivity analysis was conducted on 4,644 individuals with available smoking history data to examine the impact of smoking. The results of this analysis have been provided in the supplementary tables (Tables S2,S3).

Clinical outcomes

The primary outcome was the difference in overall mortality between patients with advanced NSCLC who did and did not use ICIs subsequently after platinum-based CC. Secondary outcomes included PFS and medical expenditure.

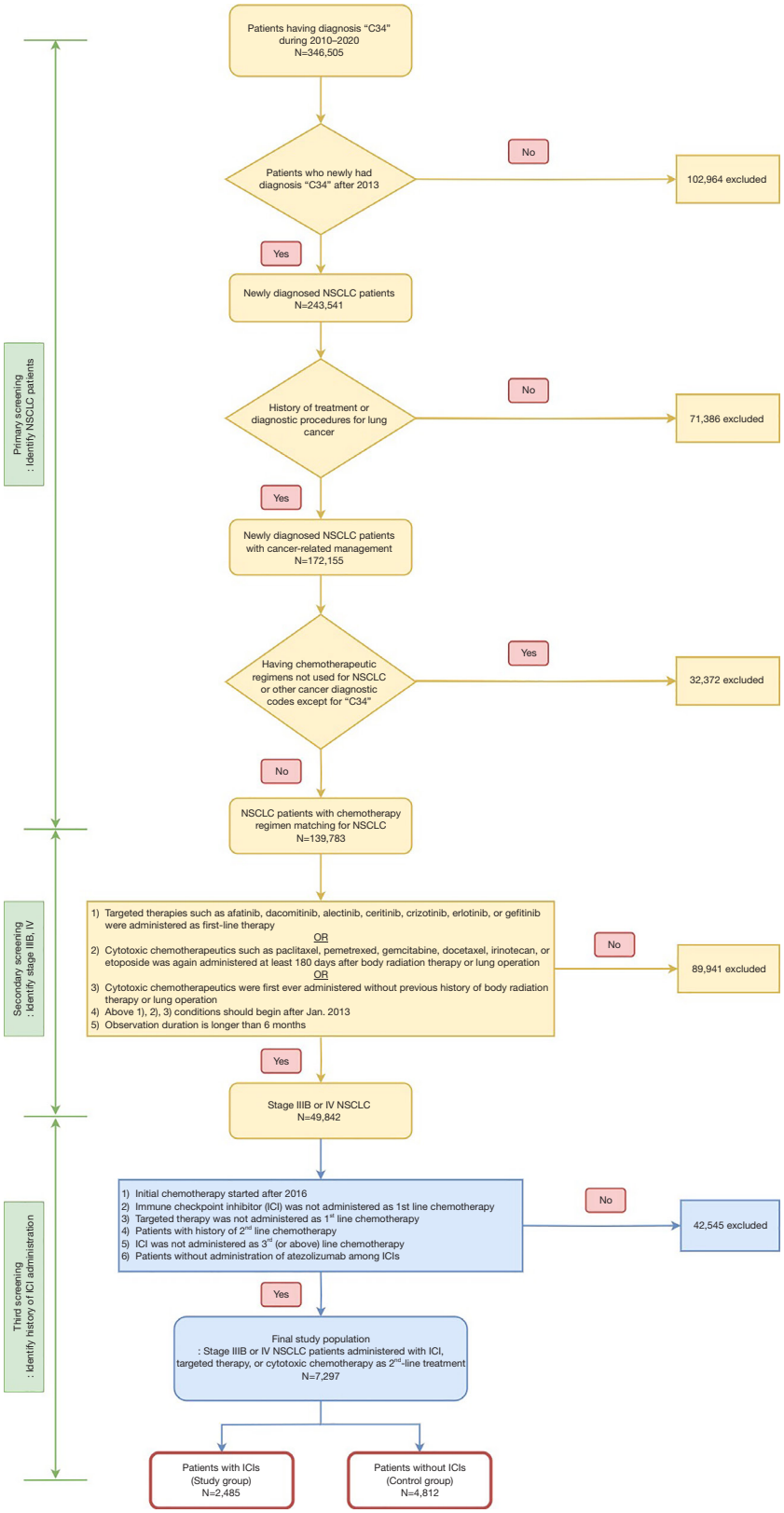

Figure 1 Flowchart of the study population. NSCLC, non-small cell lung cancer.

In the analysis related to PFS, disease progression was defined as when a patient's regimen was changed again during the secondary regimen.

Statistical analysis

The variables in each group were compared using a chi-squared test. Analysis of variance (ANOVA) was used to analyze the differences in OS, PFS, and cost differences between groups. An interrupted time series (ITS) analysis was used to evaluate the longitudinal impact of introducing a cost exemption policy. ITS is regarded as one of the most robust quasi-experimental designs to assess the effect of an intervention (22,23). In an ITS analysis, data are arranged at evenly spaced time intervals and separated into segments by the intervention. The analysis assessed the short-term impact of the intervention, as measured by a change in the level, and the over-time effect, as measured by a change in the trend (i.e., slope) after the intervention (24). Cox proportional hazard models were fitted to estimate the mortality and disease progression. The results are reported as adjusted hazard ratio (HR) with a 95% confidence interval (CI). All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) at a significance level of 5%.

Results

Baseline characteristics of the study population

Overall, 7,297 patients newly diagnosed with advanced NSCLC after 2016 were included in this study. Patients who received ICIs as second-line chemotherapeutics (n=2,485) were compared with those who did not receive ICIs (*Figure 1*). Older male patients over 60s accounted for a large proportion of both groups. The proportion of patients with stage IV disease was significantly higher in the ICI group than in the non-ICI's (98.2% *vs.* 94.7%, P<0.0001). However, the two groups did not differ significantly in income level, care level, or CCI (*Table 1*). In the ICI group, 961 and 1,524 patients were treated with nivolumab and pembrolizumab, respectively. In the non-ICI group, 3,665 and 1,147 patients received CC and TT, respectively, as second-line treatments (Table S4).

Survival outcomes

Table 2 showed survival outcomes including OS and PFS. The median OS duration was the longest in the TT group (15.5±16.7 months) and shortest in the CC group (11.2±13.2 months). In the ICI group, the median OS durations for nivolumab (11.7±12.0 months) and pembrolizumab therapy (12.9±12.3 months) were shorter than those for TT and longer than those for CC. Likewise, the PFS duration was the longest in the TT group (9.4±12.3 months) and the shortest in the CC group (6.7±9.2 months). In the ICI group, the median PFS durations for nivolumab (7.7±10.1 months) and pembrolizumab (9.0±10.9 months) therapy were shorter than those for TT and longer than those for CC. Kaplan-Meier analysis revealed that the ICI group had a significantly longer survival time than the non-ICI group. When analyzed by detailed drug, the survival time of pembrolizumab and nivolumab was longer than that of CC, and TT showed a similar survival rate to pembrolizumab (*Figure 2*). Kaplan-Meier analysis of PFS also showed that the ICI group was superior to the non-ICI group, and pembrolizumab had the highest proportion of patients with long-term survival without progression (*Figure 3*).

Risk factors associated with survival outcomes

Old age (≥60 years) and male sex were identified as risk factors for an increased risk of death. However, the ICI group had a lower risk of death than the non-ICI group (HR: 0.79; 95% CI: 0.75–0.84) (*Table 3*). Moreover, ICI group had a lower risk of disease progression than the non-ICI use group (HR 0.92; 95% CI: 0.85–0.99) (*Table 4*). When analyze with specific drugs, TT and pembrolizumab were associated with lower risks of disease progression (OR: 0.81, P<0.0001; OR: 0.81, P<0.0001) and mortality than CC (OR: 0.78, P<0.0001; OR: 0.70, P<0.0001). However, nivolumab only reduced the risk of death (OR: 0.84, P<0.0001) (Tables S5,S6).

Trends in chemotherapeutic use and medical expenses

After the NHIS-approved ICI reimbursement in 2017, the number of patients receiving ICIs following platinum chemotherapy gradually increased, while the number of patients receiving CC alone decreased (*Figure 4*). Regarding medical expenses, patients who received ICIs had higher overall medical expenses than those who did not receive them. Compared with non-ICI treatment groups, the total medical expenses were higher in patients receiving ICI treatment ($69.83K in the pembrolizumab group and

Table 1 Baseline characteristics of the total study population

Variables	Total	ICI group	Non-ICI group	P value
Total	7,297	2,485	4,812	<0.0001
Age, years (mean ± SD)	65.6±9.5	66.8±9.5	65.1±9.6	<0.0001
<40	83 (1.1)	20 (0.8)	63 (1.3)	
40–49	338 (4.6)	98 (3.9)	240 (4.9)	
50–59	1,346 (18.4)	400 (16.1)	946 (19.6)	
60–69	2,789 (38.2)	908 (36.5)	1,881 (39.0)	
≥70	2,741 (37.6)	1,059 (42.6)	1,682 (34.9)	
Sex				
Male	5,931 (81.3)	2,104 (84.6)	3,827 (79.5)	<0.0001
Female	1,366 (18.7)	381 (15.3)	985 (20.4)	
Income level				
Medical-aid	394 (5.4)	141 (5.6)	253 (5.2)	0.738
1Q	1,340 (18.4)	449 (18.0)	891 (18.5)	
2Q	1,447 (19.8)	479 (19.2)	968 (20.1)	
3Q	1,819 (24.9)	618 (24.8)	1,201 (24.9)	
4Q (richest)	2,297 (31.5)	798 (32.1)	1,499 (31.1)	
Level of care				
Secondary hospital	2,388 (32.7)	841 (33.8)	1,547 (32.1)	0.333
Tertiary hospital	4,909 (67.3)	1,644 (66.1)	3,265 (67.8)	
Comorbidity				
Hypertension	3,910 (53.5)	1,344 (54.0)	2,566 (53.3)	0.006
Diabetes	3,139 (43.0)	1,101 (44.3)	2,038 (42.3)	0.001
COPD	1,553 (21.2)	534 (21.4)	1,019 (21.1)	0.374
CKD	153 (2.0)	67 (2.7)	86 (1.7)	<0.0001
CHF	870 (11.9)	318 (12.8)	552 (11.4)	0.012
CVD	1,337 (18.3)	464 (18.6)	873 (18.1)	0.007
CCI				
6	449 (6.1)	154 (6.2)	295 (6.1)	0.440
7	783 (10.7)	269 (10.8)	514 (10.6)	
≥8	6,065 (83.1)	2,062 (82.9)	4,003 (83.1)	
Cancer stage				
Stage IIIB	295 (4.0)	44 (1.7)	251 (5.2)	<0.0001
Stage IV	7,002 (95.9)	2,441 (98.2)	4,561 (94.7)	
Brain metastasis	106 (1.4)	38 (1.5)	68 (1.4)	0.267

Data are presented as n (%) unless otherwise stated. ICI, immune checkpoint inhibitor; 1Q, first quintile; 2Q, second quintile; 3Q, third quintile; 4Q, fourth quintile (richest); COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CHF, congestive heart failure; CVD, cerebrovascular disease; CCI, Charlson comorbidity index.

Table 2 Survival outcomes and medical expenses among the study groups

Outcomes	Cytotoxic chemotherapy (N=3,665)	Targeted therapy (N=1,147)	Nivolumab (N=961)	Pembrolizumab (N=1,524)	P value*
Overall survival (months)	11.2±13.2	15.5±16.7	11.7±12.0	12.9±12.3	<0.0001
Progression-free survival (months)	6.7±9.2	9.4±12.3	7.7±10.1	9.0±10.9	<0.0001
Individual annual medical costs (USD)					
Total treatment	39.51K	41.12K	54.11K	69.83K	<0.0001
Cancer-related treatment	38.43K	39.84K	52.81K	68.53K	<0.0001

*, The P values were calculated using ANOVA (analysis of variance).

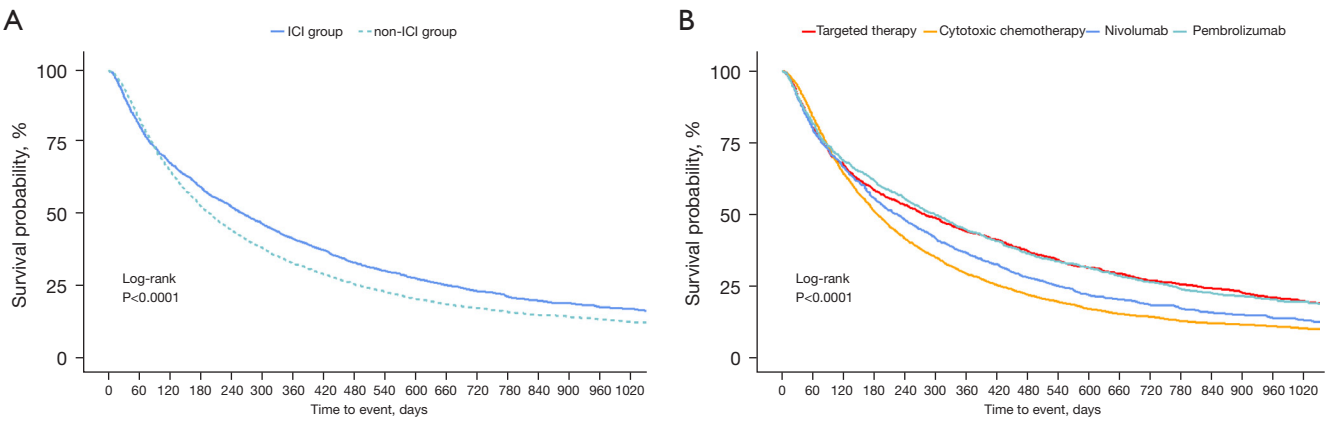

Figure 2 One-year survival rate depending on the type of second-line chemotherapeutics following platinum-based chemotherapy. (A) Immune-checkpoint inhibitors, (B) specific drugs. ICI, immune checkpoint inhibitor.

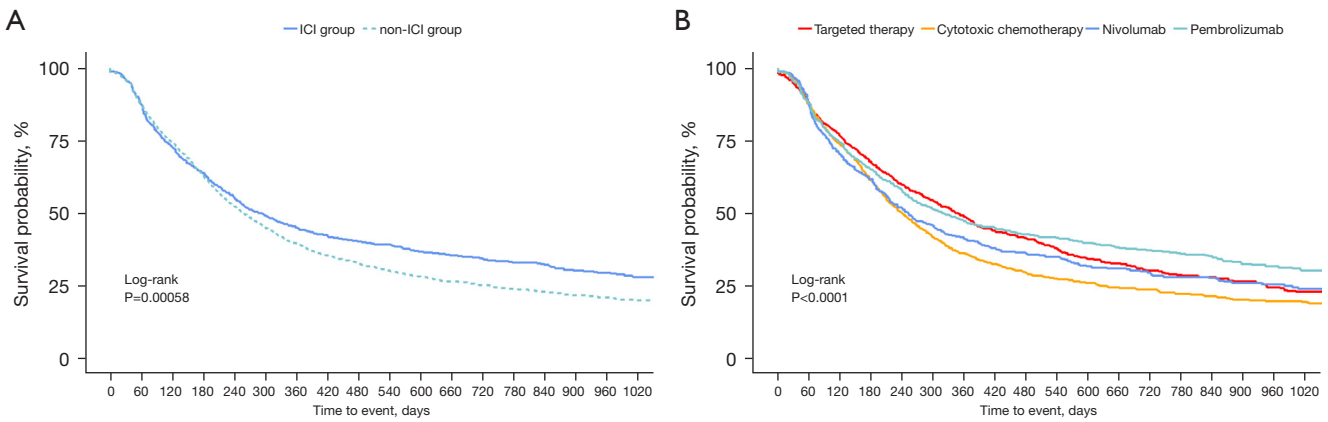

Figure 3 Progression-free survival rate depending on the type of second-line chemotherapeutics following platinum-based chemotherapy. (A) Immune-checkpoint inhibitors; (B) specific drugs. ICI, immune checkpoint inhibitor.

Table 3 Risk factors associated with all-cause mortality

Variables	Overall survival			P value
	Adjusted HR	95% CI		
		Low	High	
ICI use	0.79	0.75	0.84	<0.0001
Age (years)				
<40	Ref.			
40–49	0.97	0.74	1.27	0.828
50–59	1.11	0.86	1.42	0.403
60–69	1.28	1.00	1.64	0.044
≥70	1.48	1.16	1.90	0.001
Sex				
Male	1.27	1.18	1.36	<0.0001
Female	Ref.			
Income level				
Medical-aid	1.11	0.99	1.25	0.070
1Q	1.06	0.99	1.15	0.088
2Q	1.04	0.97	1.12	0.231
3Q	1.04	0.97	1.12	0.185
4Q (richest)	Ref.	-	-	
Type of hospital				
Secondary hospital	1.00	0.95	1.06	0.738
Tertiary hospital	Ref.			
Comorbidity				
Hypertension	1.01	0.95	1.06	0.727
Diabetes	1.03	0.97	1.09	0.259
COPD	1.02	0.96	1.09	0.404
CKD	1.14	0.96	1.36	0.120
CHF	1.01	0.93	1.09	0.806
CVD	1.01	0.94	1.08	0.662
CCI				
6	1.00			
7	0.98	0.86	1.12	0.850
≥8	0.99	0.88	1.10	0.884
Cancer stage				
Stage IIIB	Ref.			
Stage IV	1.28	1.12	1.46	0.001
Brain metastasis	0.95	0.77	1.18	0.693

HR, hazard ratio; CI, confidence interval; 1Q, first quintile; 2Q, second quintile; 3Q, third quintile; 4Q, fourth quintile (richest); ICI, immune checkpoint inhibitor; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CHF, congestive heart failure; CVD, cerebrovascular disease; CCI, Charlson comorbidity index.

Table 4 Risk factors associated with disease progression

Variables	Disease progression			P value
	Adjusted HR	95% CI		
		Low	High	
ICI use	0.92	0.85	0.99	0.035
Age (years)				
<40	Ref.	–	–	
40–49	1.03	0.75	1.40	0.841
50–59	1.00	0.75	1.34	0.971
60–69	0.91	0.68	1.22	0.547
≥70	0.74	0.55	1.00	0.050
Sex				
Male	1.01	0.93	1.10	0.689
Female	Ref.	–	–	
Income level				
Medical-aid	1.04	0.88	1.23	0.599
1Q	0.99	0.90	1.10	0.960
2Q	1.06	0.96	1.17	0.230
3Q	1.01	0.92	1.10	0.821
4Q (richest)	Ref.	–	–	
Type of hospital				
Secondary hospital	0.96	0.89	1.03	0.311
Tertiary hospital	Ref.	–	–	
Comorbidity				
Hypertension	1.03	0.96	1.12	0.340
Diabetes	0.96	0.88	1.03	0.313
COPD	0.90	0.82	0.99	0.032
CKD	0.94	0.72	1.24	0.709
CHF	0.96	0.85	1.07	0.493
CVD	0.95	0.87	1.05	0.389
CCI				
6	Ref.	–	–	
7	0.98	0.84	1.16	0.883
≥8	0.94	0.82	1.09	0.462
Cancer stage				
Stage IIIB	Ref.	–	–	
Stage IV	0.84	0.72	0.97	0.024
Brain metastasis	0.89	0.67	1.18	0.426

HR, hazard ratio; CI, confidence interval; ICI, immune checkpoint inhibitor; 1Q, first quintile; 2Q, second quintile; 3Q, third quintile; 4Q, fourth quintile (richest); COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CHF, congestive heart failure; CVD, cerebrovascular disease; CCI, Charlson comorbidity index.

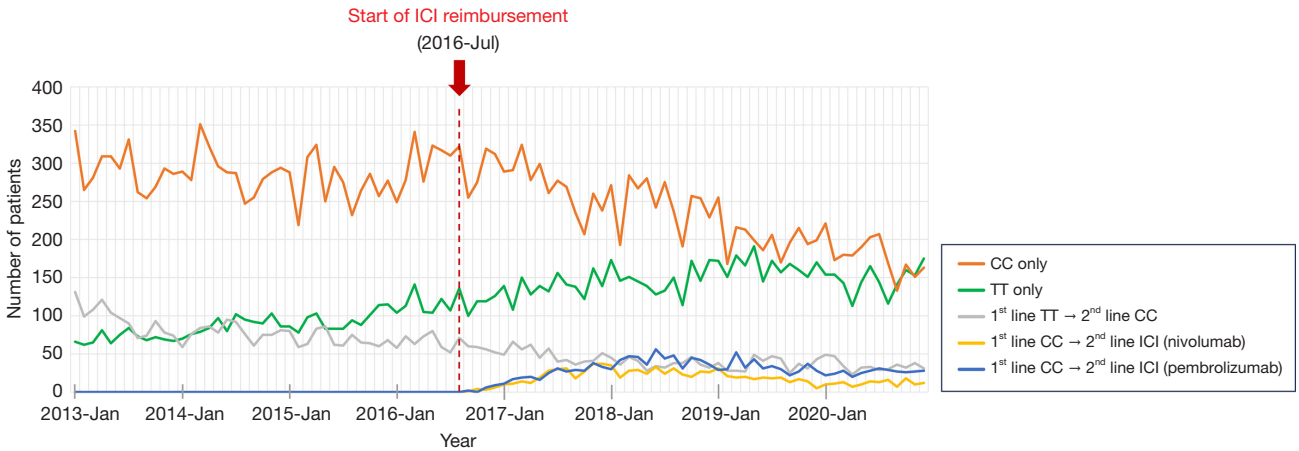

Figure 4 The trend in the number of patients according to the combination of prescribed chemotherapeutics. CC, cytotoxic chemotherapy; TT, targeted therapy; ICI, immune checkpoint inhibitor.

$54.11K in the nivolumab group) (*Table 2*). Both total and cancer-related costs increased after the introduction of reimbursement for ICIs (total cost: β, $4.56K; SE: $0.27K; P<0.0001 and cancer-related cost: β, $4.54K; SE: $0.27K; P<0.0001) (*Table 5*, *Figure 5*).

Discussion

Key findings

In this study, we found that the cost and drug retention rate among patients with NSCLC receiving second-line treatment can vary depending on the type of treatment received. ICI treatment led to longer survival and a better prognosis in terms of OS and PFS compared with CC. However, the retention rate of ICI appeared to be lower than that of TT. Additionally, when using ICIs, the increase in medical expenses for lung cancer treatment was higher than that for TT. Our study found changes in the patterns of chemotherapy drug prescriptions after coverage expanded with a significant increase in annual medical expenses per patient.

Strengths and limitations

To our knowledge, this is the first analysis of medical resource use and costs based on reimbursed claims for second-line immunotherapy for treating NSCLC in Korean patients. However, this study had some limitations. First, this was a retrospective cohort analysis of reimbursed claims data. Although predefined and strict operational definitions using diagnostic codes can help identify patients with lung cancer, they are not sufficiently detailed to accurately determine specific tumor types, disease stages, treatment responses, or adverse events. Further, there is a small possibility that stage IIIA patients who received palliative chemotherapy without definitive radiotherapy were also included in the study group. The efficacy and cost analyses did not include patients who received ICIs without reimbursement or primary treatment. In addition, considering the recent reimbursement approval, this study only analyzed the clinical efficacy and cost of immunotherapy as a secondary drug treatment. Additionally, regarding medical expenses, the cause of the cost difference was not accurately explained. However, since March 2022, the reimbursement criteria have been expanded to include ICIs as first-line therapy. The impact of this expansion on health insurance funds, including changes in prescription rates and costs, requires further analysis.

Comparison with similar research

The five-year survival update from Keynote 010 showed superior outcomes of ICI therapy for 16.9 months compared to Docetaxel for 8.2 months in programmed death-ligand 1 (PD-L1) in 50% of patients (25). Our research similarly demonstrated an OS and PFS advantage of ICI treatment over chemotherapy. However, it is important to note that our findings differ from Keynote 010's, indicating a shorter duration. This inconsistency is supported by other real-world studies (26,27), consistently aligning with our study results. Clinical trials focusing on internal validity often enroll patients with optimal organ function and good

Table 5 Interrupted time-series regression analysis of mean 1-year medical costs (USD) before and after the introduction of immune-checkpoint inhibitors

Variables	Total cost			Cancer-related cost		
	β	SE	P value	β	SE	P value
Intervention						
Before	Ref	–		Ref	–	
After	4,560.6	278.6	<0.0001	4,546.0	275.2	<0.0001
Trend before policy	52.5	8.1	<0.0001	49.0	8.0	<0.0001
Trend after policy	−4.4	12.0	0.717	−11.3	11.9	0.342
Age (years)						
<40	Ref	–		Ref	–	
40–49	−2,038.9	699.6	0.003	−2,179.1	691.0	0.001
50–59	−2,724.7	652.4	<0.0001	−2,827.5	644.3	<0.0001
60–69	−3,838.7	647.1	<0.0001	−4,004.1	639.2	<0.0001
≥70	−7,884.6	649.7	<0.0001	−8,053.8	641.7	<0.0001
Sex	3,327.6	153.6	<0.0001	3,416.5	151.7	<0.0001
Male						
Female	Ref.	–		Ref.	–	
Income level	174.0	324.6	0.591	−39.4	320.6	0.902
Medical-aid						
1Q	648.6	206.7	0.001	663.6	204.1	0.001
2Q	339.4	207.6	0.102	324.3	205.1	0.113
3Q	611.9	192.7	0.001	599.3	190.4	0.001
4Q (richest)	Ref.	–		Ref.	–	
Type of hospital						
Secondary hospital	684.8	151.6	<0.0001	671.3	149.7	<0.0001
Tertiary hospital	Ref.	–		Ref.	–	
Comorbidities						
Hypertension	407.3	162.8	0.012	300.9	160.8	0.061
Diabetes	584.8	159.0	0.0002	469.7	157.0	0.002
COPD	394.8	186.3	0.034	347.7	184.0	0.058
CKD	1,578.4	469.4	0.0008	−65.3	463.6	0.888
CHF	−2.2	233.5	0.992	−215.1	230.7	0.351
CVD	−153.9	185.2	0.406	−262.2	182.9	0.151
CCI						
6	Ref	–		Ref	–	
7	410.8	351.0	0.241	363.6	346.7	0.294
≥8	−63.8	302.4	0.832	−168.3	298.7	0.573
Cancer stage						
Stage IIIB	Ref	–		Ref	–	
Stage IV	−10,153.8	506.6	<0.0001	−10,107.7	500.4	<0.0001
Brain metastasis	84.8	568.7	0.881	205.0	561.7	0.715

SE, standard error; USD, United States dollar; 1Q, first quintile; 2Q, second quintile; 3Q, third quintile; 4Q, fourth quintile (richest); COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CHF, congestive heart failure; CVD, cerebrovascular disease; CCI, Charlson comorbidity index.

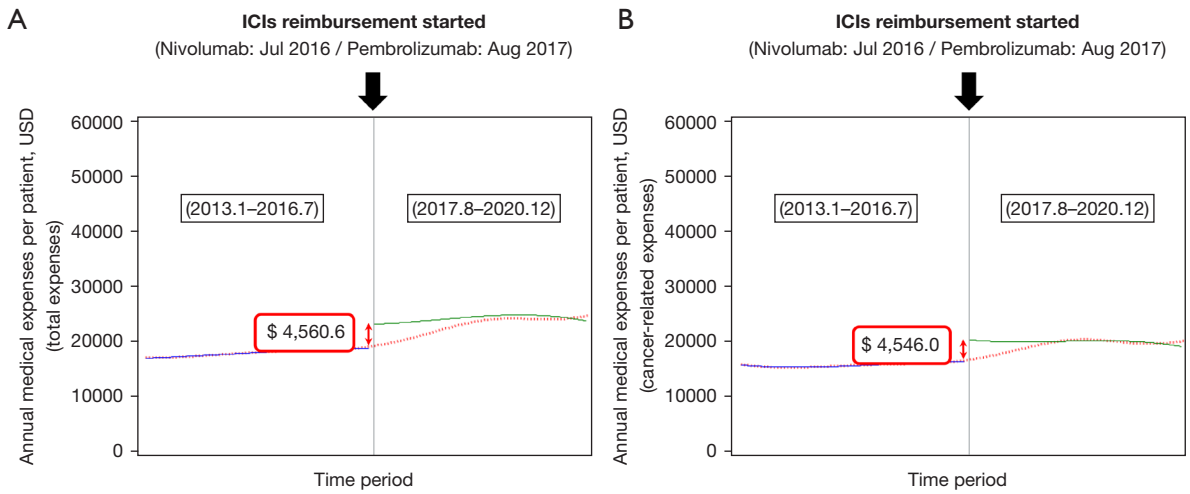

Figure 5 The trend of per capita annual medical expenses of non-small cell lung cancer patients. (A) Total expenses; (B) cancer-related expenses. ICIs, immune checkpoint inhibitors.

performance status, excluding or underrepresenting those encountered in daily practice. This creates a gap between the efficacy in randomized controlled trials and in the real world (28). Several studies have reported results similar to those of our study regarding the efficacy of ICIs according to PD-L1 testing (29-31). Khozin *et al.* analyzed claims data to examine treatment patterns and found that most patients received nivolumab and pembrolizumab in a community practice setting (31). That study also reported low rates of PD-L1 immunohistochemistry testing and a shorter PFS than that reported in pivotal trials of these therapies. However, long PFS and OS were associated with increased PD-L1 staining in previous multicenter real-world studies (32). These findings suggested that although ICIs are effective in clinical trials, there may be challenges in replicating these outcomes in real-world clinical practice. The efficacy of ICIs in patients with NSCLC is limited by a lack of strongly predictive response markers, resulting in potential underutilization of effective alternative treatments, increased risk of suboptimal care, and excessive medical care costs.

Previous studies have revealed that up to 60% of patients with NSCLC do not benefit from ICIs (14,16,33-35). The KEYNOTE-024 (33) and CheckMate-026 (36) trials investigated the efficacy of pembrolizumab and nivolumab in previously untreated patients with NSCLC. While pembrolizumab resulted in significantly longer PFS and OS than platinum-based chemotherapy in the KEYNOTE-024 trial, the CheckMate-026 trial did not show any differences in efficacy between nivolumab and chemotherapy. The KEYNOTE-024 trial used a PD-L1 threshold of ≥50%, while the CheckMate-026 trial used a cut-off of ≥1%. The effectiveness of pembrolizumab can be attributed to the selection of patients with high PD-L1 levels, inherently leading to the selection of patients who were more likely to benefit from immunotherapy than the drug itself. Therefore, patient selection is crucial for determining the success of immunotherapy, and high PD-L1 thresholds should be used to select patients who would highly benefit from PD-1/PD-L1-TT.

Explanations of findings

Our findings regarding medical expenditure differed from those of a previous study on costs and medical resource use associated with NSCLC before and after the approval of ICIs (37). The study showed that although the cost of treatment with ICIs was higher than that associated with other treatments, the total cost of care decreased following the US Food and Drug Administration's approval of ICIs, owing to a reduction in emergency room visits and hospitalizations among patients with NSCLC. Therefore, the authors concluded that although ICIs are more expensive than other drugs, they may reduce overall medical costs by reducing the use of other healthcare resources. Our study confirmed that overall medical and cancer-related medical expenses increased after reimbursement for ICIs. However, annual cancer-related medical expenses

decreased after reimbursement, although the difference was insignificant.

Implications and actions needed

Identifying potential responders to ICIs from among patients with NSCLC after identifying patients with oncogenic driver mutations in the *EGFR* and *ALK* genes is recommended because patients with these mutations have much lower response rates to ICIs and are more likely to experience increased toxicity. Accordingly, the American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines state that patients with NSCLC should receive oral therapies targeting the EGFR and ALK genes before receiving ICIs (38-40). In particular, to achieve better response rates and identify patients who will show satisfactory responses following TT, NSCLC practice guidelines recommend additional testing for a range of genetic mutations and fusions, including *ROS1* fusions, *BRAF V600E* mutations, *ERBB2 (HER2)*, and *KRAS* mutations (when part of a comprehensive panel), *NTRK1-3* and *RET* fusions, and *MET* amplification. By expanding testing beyond traditional *EGFR* and *ALK* mutations, healthcare providers can identify patients who would most likely benefit from TTs and provide personalized treatment options (38,40,41). In this context, next-generation sequencing, which is capable of determining specific genetic mutations or alterations that may drive the growth and spread of cancer, could be helpful in the management of NSCLC and may be used to develop TTs tailored to each patient's unique genetic profile.

Although the emergence of TTs and ICIs as treatment options for NSCLC has led to improved clinical outcomes in patients receiving conventional chemotherapy-based therapies, the dramatic increase in treatment-related costs for both patients and national health insurance is a potential issue. Based on the results of our study, a significantly higher medical cost was observed after ICI therapy. Therefore, extensive profiling of TTs and ICIs is essential to improve the selection and sequencing of treatments, reduce the likelihood of ineffective therapies, and enhance patient outcomes.

Conclusions

Expanding the national insurance coverage to ICIs as second-line drugs has improved clinical outcomes, including OS and PFS, in patients with advanced NSCLC. However, the results of this study indicate that the annual medical cost per patient was significantly higher in patients treated with ICIs than in those treated with TT. In contrast, the retention rates of ICIs were lower than those of TT.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-686/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the NHIS Ilsan Hospital (NHIMC 2022-10-015), and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 ICD-10 codes for the Charlson comorbidity index

Disease	Score	ICD-10 codes
Myocardial infarction	1	I21; I22; I23; I25.2; I25.3
Congestive heart failure	1	I50; I11.0; I13.0; I13.2; I25.5
Peripheral vascular disease	1	I70-I74; I731; I738; I739; I77; I771; I790; I792; K551; K558; K559; Z958; Z959; R02; K55.003; K55.004; K55.010
Cerebrovascular disease	1	I60-I63; I65; I66; G450-G452; G458; G459; G46; I64; G454; I670; I671; I672; I674; I675; I676; I677; I678; I679; I681; I682; I688; I69; I60-I69; G45; G46
Dementia	1	F00; F01; F02; F03; F051; G30; G311
Chronic pulmonary disease	1	J40-J47; J67; J60-J66; I278; I279; J684; J701; J703; J84.1; J92.0; J96.1; J98.2; J98.3; J84.9
Connective tissue disease	1	M30-M36; M332; M331; M053; M058-M060; M063; M069; M050-M052; M353; M05; M06; M315; M351; M360; M08; M09; D86
Ulcer disease	1	K25-K28; K22.1
Mild liver disease	1	B18; K700-K703; K709; K713; K715; K717; K73; K74; K760; K762-K764; K768; K769; Z944; K71.0; K71.6; K71.9; K75; K76.103; B16.9; B19.9
Diabetes mellitus	1	E109-E111; E119; E139; E101; E131; E141; E135; E100; E11.600; E120; E121; E126; E128-E131; E136; E138-E141; E146; E148; E149; E11.701
Hemiplegia	2	G81; G041; G820-G822; G114; G801; G802; G82; G830; G831-G834; G839; G838
Moderate/severe renal disease	2	N03; N052; N053; N054; N055; N056; N072; N073; N074; N01; N18; N19; N25; I120; I131; N057; Z490; Z491; Z492; Z940; Z992/I12; I13; N00-N05; N07; N11; N14; N17; Q61
Diabetes mellitus with chronic complications	2	E102; E112; E132; E142; E103; E113; E133; E143; E104; E114; E134; E144; E105; E107; E115; E122-E125; E127; E135; E137; E145; E147; E10.6; E10.8; E11.601; E11.8; E11.6; E14.5
Any tumor	2	C00-C76
Leukemia	2	C91-C95; C91.001; C95.902
Lymphoma	2	C81-C85; C88; C90; C96
Moderate/severe liver disease	3	K729; K76-K767; K721; I850; I859; I864; I982; K704; K711; B15.0; B15.9; B16.0; B16.2; B19.0; K72; I85; Z944
Metastatic solid tumor	6	C77-C80
AIDS	6	B20; B21; B22; B23; B24

ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems; AIDS, acquired immune deficiency syndrome.

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Table S2 Risk factors associated with all-cause mortality (including smoking history)

Variables	Overall survival			P value
	Adjusted HR	95% CI		
		Low	High	
ICI use	0.80	0.74	0.85	<0.0001
Age (years)				
<40	Ref.	-	-	
40-49	0.82	0.54	1.25	0.350
50-59	1.03	0.69	1.52	0.898
60-69	1.18	0.80	1.74	0.410
≥70	1.39	0.94	2.06	0.099
Sex				
Male	1.30	1.16	1.44	<0.0001
Female	Ref.	-	-	
Income level				
Medical-aid	1.15	0.94	1.41	0.165
1Q	1.08	0.98	1.18	0.115
2Q	1.11	1.01	1.21	0.031
3Q	1.10	1.01	1.20	0.025
4Q (richest)	Ref.	-	-	
Type of hospital				
Secondary hospital	1.03	0.96	1.10	0.452
Tertiary hospital	Ref.	-	-	
Comorbidity				
Hypertension	0.97	0.91	1.05	0.469
Diabetes	1.03	0.97	1.11	0.339
COPD	1.05	0.97	1.14	0.205
CKD	1.09	0.87	1.38	0.452
CHF	0.99	0.90	1.10	0.876
CVD	1.03	0.95	1.12	0.428
CCI				
6	1.00	-	-	
7	0.99	0.83	1.18	0.929
≥8	0.95	0.81	1.11	0.530
Cancer stage				
Stage IIIB	Ref.	-	-	
Stage IV	1.22	1.04	1.43	0.016
Brain mvetastasis	0.99	0.75	1.32	0.964
Smoking status				
Never-smoker	Ref.	-	-	
Ex-smoker (<10 pack-year)	0.91	0.77	1.08	0.263
Ex-smoker (≥10 pack-year)	1.07	0.97	1.18	0.180
Current smoker (<10 pack-year)	1.06	0.89	1.27	0.489
Current smoker (≥10 pack-year)	1.07	0.97	1.17	0.184

HR, hazard ratio; CI, confidence interval; ICI, immune-check point inhibitor; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CHF, congestive heart failure; CVD, cerebrovascular disease; CCI, Charlson comorbidity index; 1Q, first quintile; 2Q, second quintile; 3Q, third quintile; 4Q, fourth quintile (richest).

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Table S3 Risk factors associated with disease progression (including smoking history)

Variables	Disease progression			P value
	Adjusted HR	95% CI		
		Low	High	
ICI use	0.93	0.85	1.02	0.127
Age (years)				
<40	Ref.	-	-	-
40-49	1.09	0.66	1.79	0.736
50-59	1.07	0.66	1.72	0.790
60-69	0.98	0.61	1.56	0.916
≥70	0.79	0.49	1.28	0.339
Sex				
Male	1.09	0.94	1.25	0.250
Female	Ref.	-	-	
Income level				
Medical-aid	1.47	1.13	1.91	0.004
1Q	0.99	0.88	1.13	0.924
2Q	1.08	0.96	1.22	0.203
3Q	1.00	0.90	1.12	0.955
4Q (richest)	Ref.	-	-	
Type of hospital				
Secondary hospital	1.01	0.92	1.10	0.894
Tertiary hospital	Ref.	-	-	
Comorbidity				
Hypertension	1.01	0.92	1.11	0.816
Diabetes	0.99	0.91	1.09	0.899
COPD	0.91	0.81	1.01	0.087
CKD	0.82	0.57	1.18	0.284
CHF	0.90	0.78	1.04	0.139
CVD	1.02	0.91	1.15	0.730
CCI				
6	Ref.	-	-	
7	1.09	0.87	1.36	0.454
≥8	0.98	0.81	1.20	0.867
Cancer stage				
Stage IIIB	Ref.	-	-	
Stage IV	0.84	0.70	1.02	0.071
Brain metastasis	0.83	0.56	1.22	0.332
Smoking status				
Never-smoker	Ref.	-	-	-
Ex-smoker (<10 pack-year)	0.97	0.78	1.21	0.779
Ex-smoker (≥10 pack-year)	0.97	0.84	1.11	0.662
Current smoker (<10 pack-year)	0.94	0.75	1.18	0.575
Current smoker (≥10 pack-year)	0.95	0.84	1.09	0.482

HR, hazard ratio; CI, confidence interval; ICI, immune-check point inhibitor; 1Q, first quintile; 2Q, second quintile; 3Q, third quintile; 4Q, fourth quintile (richest); COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CHF, congestive heart failure; CVD, cerebrovascular disease; CCI, Charlson comorbidity index.

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Table S4 Baseline characteristics of the total study population (grouped by specific drugs)

Variables	Total (N=7,297)	Non-ICI therapy		ICI therapy		P value
		Targeted therapy (N=1,147)	Cytotoxic chemotherapy (N=3,665)	Nivolumab (N=961)	Pembrolizumab (N=1,524)	
Age (mean ± SD)		64.8±10.9	65.2±9.1	67.4±9.2	66.4±9.6	<0.0001
<40	83 (1.1)	26 (2.2)	37 (1.0)	4 (0.4)	16 (1.0)	<0.0001
40-49	338 (4.6)	84 (7.3)	156 (4.2)	30 (3.1)	68 (4.4)	
50-59	1,346 (18.4)	234 (20.4)	712 (19.4)	148 (15.4)	252 (16.5)	
60-69	2,789 (38.2)	366 (31.9)	1,515 (41.3)	345 (35.9)	563 (36.9)	
≥ 70	2,741 (37.6)	437 (38.1)	1,245 (33.9)	434 (45.1)	625 (41.0)	
Sex						
Men	5,931 (81.3)	718 (62.6)	3,109 (84.8)	808 (84.0)	1,296 (85.0)	0.857
Women	1,366 (18.7)	429 (37.4)	556 (15.1)	153 (15.9)	228 (14.9)	
Income level						
Medical-aid	394 (5.4)	60 (5.2)	193 (5.2)	63 (6.5)	78 (5.1)	0.118
1Q	1,340 (18.4)	224 (19.5)	667 (18.2)	173 (18.2)	276 (18.1)	
2Q	1,447 (19.8)	218 (19.0)	750 (20.4)	192 (19.9)	287 (18.8)	
3Q	1,819 (24.9)	284 (24.7)	917 (25.0)	230 (23.9)	388 (25.4)	
4Q (richest)	2,297 (31.5)	361 (31.4)	1,138 (31.0)	303 (31.5)	495 (32.4)	
Level of care						
Secondary hospital	2,388 (32.7)	391 (34.0)	1,156 (31.5)	313 (32.5)	528 (34.6)	0.118
Tertiary hospital	4,909 (67.3)	756 (65.9)	2,509 (68.4)	648 (67.4)	996 (65.3)	
Comorbidity						
Hypertension	3,910 (53.5)	589 (51.3)	1,977 (53.9)	533 (55.4)	811 (53.2)	0.268
Diabetes	3,139 (43.0)	445 (38.8)	1,593 (43.4)	428 (44.5)	673 (44.1)	0.015
COPD	1,553 (21.2)	177 (15.4)	842 (22.9)	229 (23.8)	305 (20.0)	<0.0001
CKD	153 (2.0)	19 (1.6)	67 (1.8)	25 (2.6)	42 (2.7)	0.078
CHF	870 (11.9)	116 (10.1)	436 (11.9)	126 (13.1)	192 (12.6)	0.136
CVD	1,337 (18.3)	192 (16.7)	681 (18.5)	197 (20.5)	267 (17.5)	0.122
CCI						
6	449 (6.1)	96 (8.3)	199 (5.4)	51 (5.3)	103 (6.7)	<0.0001
7	783 (10.7)	147 (12.8)	367 (10.0)	100 (10.4)	169 (11.0)	
≥8	6,065 (83.1)	904 (78.8)	3,099 (84.5)	810 (84.2)	1,252 (82.1)	
Cancer stage						
Stage IIIB	295 (4.0)	33 (2.8)	218 (5.9)	16 (1.6)	28 (1.8)	<0.0001
Stage IV	7,002 (95.9)	1,114 (97.1)	3,447 (94.0)	945 (98.3)	1,496 (98.1)	
Brain metastasis	106 (1.4)	15 (1.3)	53 (1.4)	11 (1.1)	27 (1.7)	0.595

ICI, immune-check point inhibitor; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CHF, congestive heart failure; CVD, cerebrovascular disease; CCI, Charlson comorbidity index; 1Q, first quintile; 2Q, second quintile; 3Q, third quintile; 4Q, fourth quintile (richest).

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Table S5 Risk factors associated with all-cause mortality (grouped by specific drugs)

Variables	Overall survival			P-value
	Adjusted OR	95% CI		
		Low	High	
Type of chemotherapeutics				
Cytotoxic chemotherapy	Ref.	-	-	
Targeted therapy	0.78	0.73	0.85	<0.0001
Nivolumab	0.84	0.78	0.91	<0.0001
Pembrolizumab	0.70	0.65	0.75	<0.0001
Age (years)				
<40	Ref.	-	-	
40-49	0.95	0.73	1.25	0.740
50-59	1.07	0.83	1.37	0.572
60-69	1.23	0.96	1.57	0.098
≥70	1.42	1.11	1.82	0.004
Sex				
Men	1.22	1.14	1.307	<0.0001
Women	Ref.	-	-	
Income level				
Medical-aid	1.10	0.98	1.24	0.085
1Q	1.07	0.99	1.15	0.073
2Q	1.04	0.96	1.12	0.279
3Q	1.04	0.97	1.11	0.193
4Q (richest)	Ref.	-	-	
Type of hospital				
Secondary hospital	1.01	0.96	1.07	0.583
Tertiary hospital	Ref.	-	-	
Comorbidity				
Hypertension	1.01	0.96	1.07	0.580
Diabetes	1.03	0.97	1.08	0.305
COPD	1.01	0.95	1.08	0.639
CKD	1.16	0.97	1.38	0.086
CHF	1.00	0.92	1.08	0.911
CVD	1.00	0.94	1.07	0.807
CCI				
6	Ref.	-	-	
7	0.98	0.86	1.11	0.765
≥8	0.97	0.86	1.08	0.615
Cancer stage				
Stage IIIB	Ref.	-	-	
Stage IV	1.30	1.14	1.48	<0.0001
Brain metastasis	0.96	0.77	1.19	0.727

COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CHF, congestive heart failure; CVD, cerebrovascular disease; CCI, Charlson comorbidity index; 1Q, first quintile; 2Q, second quintile; 3Q, third quintile; 4Q, fourth quintile (richest).

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Table S6 Risk factors associated with disease progression (grouped by specific drugs)

Variables	Disease progression			P-value
	Adjusted OR	95% CI		
		Low	High	
Type of chemotherapeutics				
Cytotoxic chemotherapy	Ref.	-	-	
Targeted therapy	0.81	0.73	0.89	<0.0001
Nivolumab	0.99	0.89	1.10	0.926
Pembrolizumab	0.81	0.74	0.89	<0.0001
Age (years)				
<40	Ref.	-	-	
40-49	1.01	0.74	1.38	0.914
50-59	0.98	0.73	1.30	0.891
60-69	0.88	0.66	1.17	0.393
≥70	0.72	0.54	0.96	0.029
Sex				
Men	0.97	0.89	1.06	0.601
Women	Ref.	-	-	
Income level				
Medical-aid	1.04	0.87	1.23	0.650
1Q	1.00	0.90	1.10	0.975
2Q	1.05	0.95	1.16	0.263
3Q	1.01	0.92	1.10	0.826
4Q (richest)	Ref.	-	-	
Type of hospital				
Secondary hospital	0.96	0.89	1.03	0.353
Tertiary hospital	1.00	-	-	
Comorbidity				
Hypertension	1.04	0.96	1.12	0.260
Diabetes	0.96	0.88	1.03	0.306
COPD	0.89	0.81	0.97	0.015
CKD	0.95	0.72	1.24	0.715
CHF	0.95	0.85	1.07	0.442
CVD	0.95	0.86	1.04	0.313
CCI				
6	Ref.	-	-	
7	0.98	0.83	1.15	0.832
≥8	0.93	0.80	1.07	0.315
Cancer stage				
Stage IIIB	1.00	-	-	
Stage IV	0.85	0.73	0.99	0.036
Brain metastasis	0.89	0.67	1.18	0.434

COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CHF, congestive heart failure; CVD, cerebrovascular disease; CCI, Charlson comorbidity index; 1Q, first quintile; 2Q, second quintile; 3Q, third quintile; 4Q, fourth quintile (richest)

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