Cost-effectiveness analysis of pembrolizumab with chemotherapy for metastatic nonsquamous non-small cell lung cancer in Taiwan

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Abstract

This study was aimed to evaluate the cost-effectiveness of pembrolizumab with chemotherapy (pembrolizumab combination therapy) and compare it with standard-of-care platinum-based chemotherapy (chemotherapy alone) as a first-line treatment for metastatic nonsquamous NSCLC from the perspective of Taiwan's third-party-payer public health-care system. We used a partitioned survival model with an estimated time horizon of 10 years. The partitioned survival model uses Kaplan−Meier estimates of progression-free and overall survival from the KEYNOTE-189 clinical trial. The quality-adjusted life-year (QALY) values were based on utility values by progression status calculated from the KEYNOTE-189 trial. This study examined costs related to treatment regimens, disease management, second-line therapy, end-of-life care, and adverse event management. Cost and utility were discounted at 3% per year. Probabilistic and deterministic sensitivity analyses were performed to test the robustness of the results. The willingness-to-pay threshold was set at 3 × Taiwan's gross domestic product (GDP), equivalent to NT$2,788,290. In the base-case scenario, pembrolizumab combination therapy resulted in an expected gain of 0.89 QALYs and an incremental cost of NT$2,201,203 relative to chemotherapy alone. The ICER was NT$2,478,601/QALY. In the analysis of the PD-L1 tumor proportion score (TPS) ≥ 50% subgroup, the patients who received pembrolizumab combination therapy gained 1.12 QALYs more than those who received chemotherapy alone, and the incremental cost was NT$2,522,528. Therefore, the ICER for this subset of patients was NT$2,258,358/QALY. In conclusion, pembrolizumab combination therapy is a cost-effective option for first-line treatment of metastatic nonsquamous NSCLC. The relative cost-effectiveness of pembrolizumab combination therapy is greatest for patients with PD-L1 TPS ≥50%.

Keywords: Cost effectiveness analysis, Nonsquamous non-small-cell lung cancer, Pembrolizumab plus chemotherapy, Pharmacoeconomics, Programmed cell death ligand 1

1. Introduction

Lung cancer is the third most common cancer and the leading cause of cancer-related death in Taiwan, with non-small-cell lung cancer (NSCLC) being the most common type of all lung cancer [1−3]. Approximately 50% of lung cancer cases have distant metastases at diagnosis, and the 5-year survival rate is just 5.5% [4−6]. However, significant progress has been made in treating metastatic NSCLC [7−9]. Pembrolizumab became the first PD-1 immune checkpoint inhibitor approved by the

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United States (US) Food and Drug Administration in September 2014 for the initial treatment of metastatic NSCLC in patients with tumors expressing programmed cell death ligand 1 (PD-L1) but no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) aberrations and with disease progression during or after platinum-based doublet chemotherapy [10,11]. In 2018, pembrolizumab combined with pemetrexed and platinum was approved for patients with advanced nonsquamous NSCLC without EGFR/ALK variants [12,13]. After that, the KEYNOTE-189 trial demonstrated that pembrolizumab combined with pemetrexed/platinum chemotherapy is able to significantly prolong the progression-free survival (PFS) and overall survival (OS) of patients with NSCLC [14]. Therefore, the 2021 National Comprehensive Cancer Network guidelines recommended pembrolizumab combination therapy as a first-line treatment option for patients with metastatic nonsquamous NSCLC, no contraindications to PD-1 or PD-L1 inhibitors, and no driver variants, regardless of their PD-L1 levels [15,16].

National Health Insurance (NHI) in Taiwan reimburses pembrolizumab monotherapy for the first-line treatment of metastatic NSCLC for patients who are unfit for chemotherapy and have a PD-L1 tumor proportion score (TPS) $\geq$ 50%. For patients with PD-L1 TPS <50%, the NHI only reimburses for chemotherapy alone. The combination of pembrolizumab with chemotherapy is not reimbursed. Pembrolizumab is administered every 3 weeks at a fixed dose of 200 mg [17]. According to the price announced by the NHI of Taiwan in January 2021, the average monthly cost of pembrolizumab therapy is approximately NT$190,728. Although pembrolizumab combination therapy was considered as effective for treating metastatic NSCLC, the high price is still the primary concern. In this study, we evaluated the cost-effectiveness of pembrolizumab combination therapy as a first-line treatment for advanced NSCLC patients in Taiwan.

2. Methods

This study was conducted in accordance with the Consolidated Health Economic Evaluation Reporting Standards [18].

2.1. Model overview

A partitioned survival analysis model was developed to assess the cost-effectiveness of pembrolizumab combination therapy compared with chemotherapy alone using TreeAge Pro Healthcare software (version 2021) [19–21]. In KEYNOTE-189 study, the study group is pembrolizumab combination and the comparison group is chemotherapy alone. It was compatible with our study exploration. In addition, Horinouchi et al. analyzed data of Japanese population subgroup in KEYNOTE-189 and demonstrated similar efficacy and safety [22]. ESMO Pan-Asia adapted guideline also recommends the combination regimen for patients with stage IV NSCLC [23]. Therefore, we constructed the microsimulation model and the Kaplan–Meier (KM) estimates of PFS and OS from the KEYNOTE-189 trial for evaluating the health and cost outcomes of patients with advanced metastatic nonsquamous NSCLC from the perspective of Taiwan's NHI Administration [14]. These parameters were collected for the entire trial population and subgroups of patients with PD-L1 TPSs of $\geq$50%, 1%–49%, and <1%. The model accounted for three mutually exclusive health states: the PF state, the progressed disease (PD) state, and death (Fig. 1) [19]. The initial health state of every patient entering the trial was assumed to be the PF state. The survival curve was used to estimate the probability of remaining in certain health states over time. The transition from PF to PD would be calculated as the difference between the OS and PFS. Because pembrolizumab may have a long term effect, we used a 1-year cycle length to simulate for a 10-year time horizon with a discount rate of 3% annually for all health and cost outcomes [24,25]. For maintenance pembrolizumab and pemetrexed, we set the maximum number of chemotherapy cycles as 17 per year.

2.2. Treatment details

As a reference, we selected the clinical treatment options for advanced nonsquamous NSCLC in

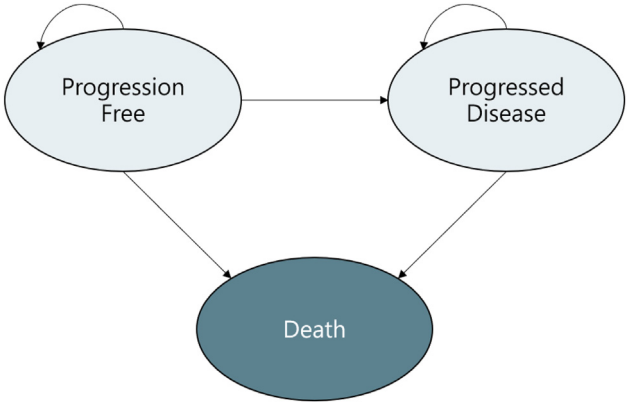

*Fig. 1. **Diagram of Transitions Between Health States.** Arrows represent transitions between health states.*

Taiwan from the KEYNOTE-189 trial and modified them according to the following treatment plan. In the PF state, all patients received either pembrolizumab combination therapy (pemetrexed 500 mg/m^2, cisplatin 75 mg/m^2, and pembrolizumab 200 mg) or chemotherapy alone (pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2) as a first-line treatment once every 3 weeks for four cycles. After four cycles, the pembrolizumab combination and chemotherapy alone groups used pembrolizumab (200 mg) plus pemetrexed (500 mg/m^2) and pemetrexed (500 mg/m^2) alone, respectively, every 3 weeks for a total of 31 cycles [14,17].

Second-line treatments for patients in the PD state were selected from KEYNOTE-189 trial data regarding subsequent therapies that were applied with a frequency of ≥1%. We selected treatment options reimbursed by NHI only and then used the percentage of the selected treatments in KEYNOTE-189 as a reference ratio to calculate the proportions of each second-line treatment in our analysis (Supplementary Table 1 (https://doi.org/10.38212/2224-6614.3536) [14].

2.3. Model probabilities and health state utilities

The patients' probabilities of transitioning between health states were based on the survival curves from the KEYNOTE-189 trial. We used DigitizeIt (V.2.5) software to reconstruct KM curves for OS and PFS over 30 months and fitted the model using the Bayesian simulation method in the R studio survHE package [26–28]. The Akaike information criterion (AIC), Bayesian information criterion (BIC), and visual inspection method were applied to determine the distribution of extrapolation for a 10-year horizon (Supplementary Table 2 (https://doi.org/10.38212/2224-6614.3536)) [29]. We fitted nine parametric survival models and then calculated the AIC and BIC to measure the goodness-of-fit of the models. The models with the lowest AIC and BIC and better visual fit were determined as the final extrapolation distribution.

Treatment effectiveness was measured in quality-adjusted life-years (QALYs) and was the weighted average of the utility values for the entire period. The utility values ranged from 0 to 1, with 1 representing perfect health and 0 representing death [30]. We adopted the KEYNOTE-189 trial's utility values for the progression-based health state [31].

2.4. Costs

Only direct costs were considered in our study design. The expenses associated with cancer treatment consist of per-cycle and one-time costs. Here, the per-cycle costs included drug administration, second-line treatment, and disease management, and the one-time costs included PD-L1 tests, end-of-life care, and adverse event (AE) management [32–35]. The medication unit prices were calculated using the prices announced by the NHI Administration in January 2021. The patients' average height and weight were calculated to be 158.5 cm and 62.3 kg, respectively [36]. Hence, our study used a 1.6 m^2 body surface area for total dose calculation. We adjusted the total doses of pemetrexed and cisplatin in each course to 800 and 100 mg, respectively, on the basis of recommendations of Taiwanese clinical experts. The drug administration costs included cytotoxic drug administration and premedication (Supplementary Table 3 (https://doi.org/10.38212/2224-6614.3536)). The disease management cost was NT$ 91,810 based on a study of cancer economic burden in Taiwan and calculate once per year [37]. The cost of end-of-life was NT$392,820 based on the Taiwan's NHI yearly report in 2018 and counted once when patients left the model [38]. Because high-grade AEs are of great concern to clinicians, we selected AEs above grade 3 that occurred in the KEYNOTE-189 trial with a frequency of ≥5% to calculate the costs associated with AEs (Supplementary Table 4 (https://doi.org/10.38212/2224-6614.3536)) [39]. Pneumonitis was also included in the assessment of AE-associated costs because it is a common complication of pembrolizumab therapy [40]. We calculate the medication costs of these AEs and weighted by the incidence rates reported in the KEYNOTE-189 trial. The cost of AE management would be counted once when patients transitioned from PF to PD state.

2.5. Sensitivity analysis

Cost-effectiveness was measured using incremental cost-effectiveness ratios (ICERs), which are commonly used to evaluate the cost-effectiveness of health-care interventions. We defined the willingness-to-pay (WTP) threshold as NT$2,788,290, which was triple Taiwan's annual gross domestic product (GDP) per capita in 2021 [41]. We conducted one-way deterministic sensitivity analyses by changing one parameter at a time and keeping all the other variables constant to assess the effect of each parameter on the cost-effectiveness of the treatments [42]. The cost variation range was ±25%, and the cost variation range for AEs was ±50%. Tornado diagrams were used to visualize the results. We performed a probabilistic sensitivity analysis (PSA) using the Monte Carlo method by

conducting 10,000 repeated simulations to test the robustness of our findings by changing all the variables simultaneously [43]. The beta distribution was applied to health utilities, and a uniform distribution was applied for cost. Cost-effectiveness acceptability curves were used to visualize the results. Additionally, we conducted a subgroup analysis according to PD-L1 TPS (≥50%, 1%–49%, and ≤1%). We also adjusted the length of treatment to 5 and 20 years as a scenario analysis considering short term impact and long term effect.

3. Results

3.1. Base-case analysis

The parameters we used for the cost-effectiveness analysis model and the results of the extrapolated survival analysis are presented in Table 1 and Fig. 2. According to the base-case analysis, the average annual cost of pembrolizumab combination therapy is NT$4,145,237 in Taiwan. The cost is higher than that of chemotherapy alone (NT$1,944,034). Patients who received pembrolizumab combination therapy gained 0.89 more QALYs than those who received chemotherapy alone (1.95 vs. 1.07 QALYs, respectively). The differences between these groups yielded an ICER of NT$2,478,601 per QALY, which was cost-effective at a WTP threshold of NT$2,788,290 (Table 2).

3.2. Sensitivity analysis

As shown in Fig. 3, the tornado diagram illustrates the results of one-way sensitivity analysis, displaying the range of ICER values obtained by adjusting the parameters. The factor most strongly influencing the ICER was the cost of pembrolizumab combination therapy from the 5th to 31st cycles, for which the corresponding ICER values ranged from NT$2,158,392 to NT$3,597,320 per QALY. The cost of PD-L1 testing, the discount rate, and the cost of AE management exhibited limited effects on the model. Furthermore, the cost-effectiveness acceptability curves provided the results of PSA at different WTP thresholds (Supplementary Fig.1. (https://doi.org/10.38212/2224-6614.3536)). At a WTP threshold of NT$2,230,632 per QALY, chemotherapy is a cost-effective option for 99.99% of patients. When the WTP threshold increased to NT$2,650,000 per QALY, the cost-effectiveness probabilities for both groups were equal. Notably, at the WTP threshold of triple Taiwan's GDP (NT$2,788,290), pembrolizumab combination therapy is cost-effective for approximately 70% of patients.

3.3. Subgroup analysis

PD-L1 has been considered a critical biomarker to predict the therapeutic outcomes of immune checkpoint inhibitors. Therefore, we conducted a subgroup analysis by dividing the patients into three groups according to their PD-L1 TPS, namely ≥50%, 1%–49%, and <1%, and the ICER values for these groups were NT$2,258,358/QALY, NT$2,624,878/QALY, and NT$2,501,406/QALY, respectively (Table 2). If the WTP threshold is triple that of Taiwan's GDP (NT$2,788,290), pembrolizumab combination therapy is cost-effective for 92.6%, 79.5%, and 90.4% of patients in the groups of TPS: ≥50%, 1%–49%, and <1%, respectively. Additionally, we adjusted ICER values for the treatment length between 5 and 20 years. The ICER values for patients were

Table 1. Parameters for cost-effectiveness model.

Parameter	Pembrolizumab combination therapy	Chemotherapy alone	Distribution	Source
Extrapolation simulation				
Overall survival	Weibull (AFT)	Log-normal		
Progression-free survival	Log-logistic	Log-normal		
Utility				
Progression-free	0.768 (0.759, 0.777)	0.757 (0.742, 0.771)	Beta	KN189
Progressed disease	0.710 (0.681, 0.740)	0.645 (0.600, 0.689)	Beta	KN189
Cost[a](NT$)	Value	Value		
Treatment-related costs				
1–4 cycles	3,011,056	722,320	Uniform	NHIA
5–31 cycles	2,877,856	589,120	Uniform	NHIA
>31 cycles	589,120	589,120	Uniform	NHIA
Second-line treatment	381,216	1,070,964	Uniform	NHIA
PD-L1 testing	5984	5984	Uniform	NHIA
Disease management	91,812	91,812	Uniform	[37]
End-of-life care	392,820	392,820	Uniform	[38]
Adverse events	2192	1714	Uniform	[54–57]

AFT, Accelerated failure time; NHIA, National Health Insurance Administration.

[a] All costs was tested for sensitivity and the variation range was ±25%. Only the cost variation range for AEs was ±50%.

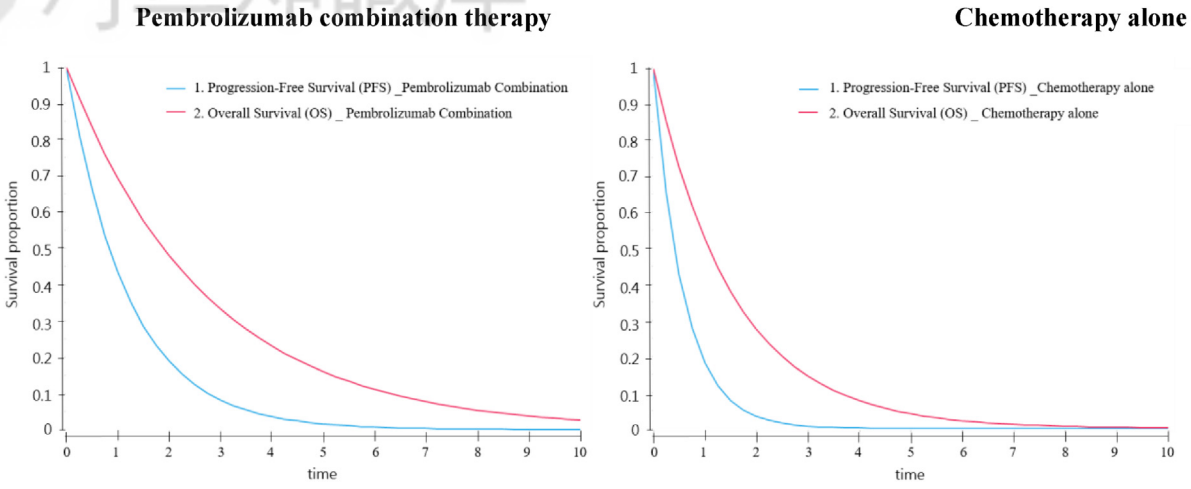

Fig. 2. ***Reconstructed and Extrapolated Kaplan–Meier Survival Curves.*** *We reconstructed the survival curves from the KEYNOTE-189 trial (30 months) and extrapolated them to 10 years.*

NT$3,089,018/QALY (5 years) and NT$2,390,320/QALY (20 years) (Table 2).

4. Discussion

In this study, we applied the health-care system in Taiwan as a model to compare the cost-effectiveness of pembrolizumab in combination with chemotherapy and chemotherapy alone as first-line treatment for patients with metastatic NSCLC. Our results indicated that pembrolizumab combination therapy's ICER is NT$2,478,601/QALY. Pembrolizumab combination therapy is a cost-effective treatment option when using Taiwan's NHI

Table 2. Base case and subgroup/scenario analysis summary.

Outcome	Pembrolizumab combination therapy	Chemotherapy alone	Incremental pembrolizumab combination therapy vs. chemotherapy alone
Base case			
Cost	NT$4,145,237	NT$1,944,034	NT$2,201,203
QALY	1.95	1.07	0.89
ICER			NT$2,478,601/QALY
TPS			
PD-L1 TPS ≥ 50%			
Cost	NT$4,941,799	NT$2,419,271	NT$2,522,528
QALY	2.45	1.33	1.12
ICER			NT$2,258,358/QALY
PD-L1 TPS 1%–49%			
Cost	NT$4,203,497	NT$1,970,201	NT$2,233,296
QALY	1.96	1.11	0.85
ICER			NT$2,624,878/QALY
PD-L1 TPS <1%			
Cost	NT$3,346,613	NT$1,536,373	NT$1,810,240
QALY	1.55	0.83	0.72
ICER			NT$2,501,406/QALY
Time horizon			
Time horizon of 5 years			
Cost	NT$3,915,306	NT$1,857,376	NT$2,057,930
QALY	1.69	1.03	0.66
ICER			NT$3,089,018/QALY
Time horizon of 20 years			
Cost	NT$4,188,726	NT$1,948,100	NT$2,240,626
QALY	2.00	1.07	0.94
ICER			NT$2,390,320/QALY

QALY, quality-adjusted life-year.
ICER, incremental cost-effectiveness ratio.

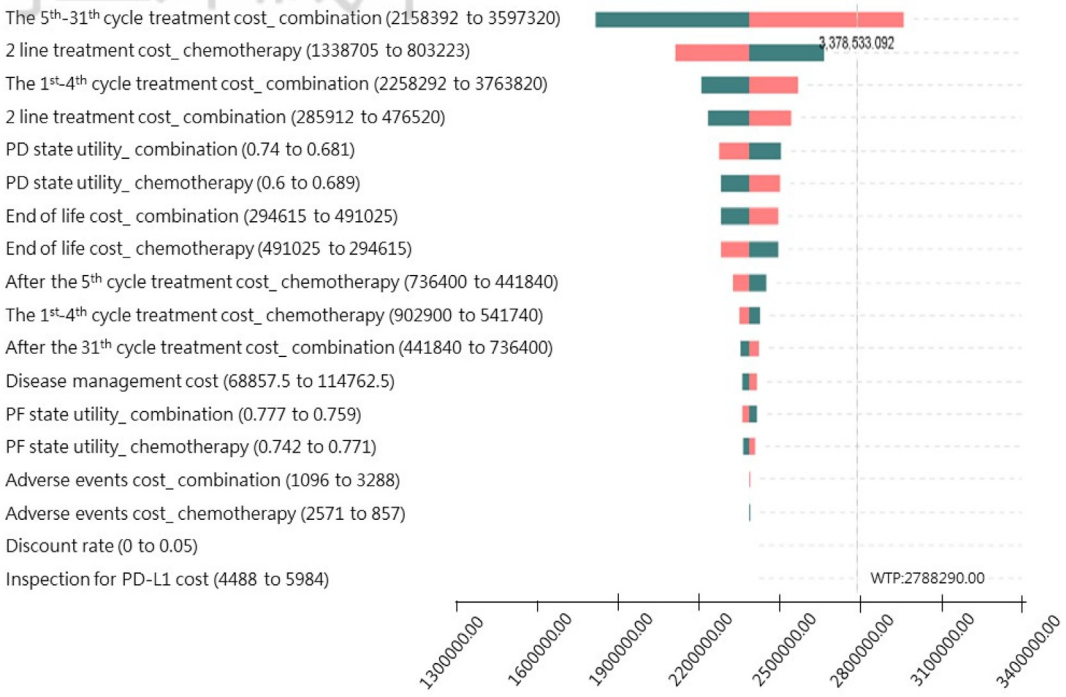

Fig. 3. ***Deterministic Sensitivity Analysis for Base Case: Pembrolizumab Combination Therapy Versus Chemotherapy Alone.*** *The gray line represents the NT$2,788,290 per quality-adjusted life-year (QALY) willingness-to-pay threshold used in this study. The lower and upper bounds in the sensitivity analysis are parenthesized after each variable. ICER: incremental cost-effectiveness ratio.*

program's WTP threshold, especially for patients with tumors with PD-L1 TPSs of ≥50%.

Several studies have reported the economic impacts of different pembrolizumab-containing regimens for NSCLC [32,33,44]. Data from the KEYNOTE-189 trial were applied to conduct a cost-effectiveness analysis from the perspective of US third-party health-care payers. For example, Insinga et al. inputted individual data into their partitioned survival model and used the time-to-death utility from the KEYNOTE-189 trial. Their results indicated that the pembrolizumab combination group gained 1.44 more QALYs than the chemotherapy alone group but incurred an extra cost of $150,888, and the ICER was $104,823/QALY. The results supported the cost-effectiveness of pembrolizumab combination therapy when compared with WTP thresholds of $100,000−$150,000 in the United States. Zeng et al. used Markov model analysis and extracted utility values from the data collected by one study designed to elicit UK societal-based utility values for different stages of NSCLC and different grade III−IV toxicities commonly associated with chemotherapy treatments [45]. The results indicated that the pembrolizumab combination group gained 0.78 more QALYs than the chemotherapy alone group but incurred an extra cost of $151,409, and the ICER was $194,372/QALY, which indicated that the treatment was not cost-effective. Although the costs of the treatments in the two studies were similar, the QALY values differed significantly due to different methods used for utility estimation, leading to different conclusions. Our methodology differs from that of other studies in several respects. First, we followed the National Institute for Health and Care Excellence guidelines and used a partitioned survival model for analyzing advanced or transitional cancer [46,47]. Unlike the Markov model that determines a patient's transition probability according to the median survival curve, the partitioned survival model uses each survival curve time point directly. This method can reflect the state of cancer progression more accurately. In addition, we adopted the utility values for different health conditions from the KEYNOTE-189 trial. Concerning the difference of time-to-death utility between two groups was larger [31], if we can obtained individual data then the intergroup differences in utility values would have been more pronounced, the ICERs would have been lower, and the calculated cost-effectiveness of pembrolizumab combination therapy would have been higher.

Here, we conducted one-way sensitivity analysis. The results indicated that pembrolizumab cost significantly affected the cost-effectiveness of pembrolizumab combination therapy. The dose of

pembrolizumab in earlier trials in NSCLC was 2 mg/kg [48,49]. According to the pharmacokinetic literature, pembrolizumab exposure at 200 mg every 3 weeks is similar to that of 2 mg/kg every 3 weeks for the treatment of advanced NSCLC [50]. The dose of pembrolizumab in KEYNOTE-189 was 200 mg. If we used a weight-based dosage, then it was comparable to the dosage for patients with a body weight of 100 kg. Pembrolizumab was previously formulated in two strengths: 50 and 100 mg/vial. However, only 100-mg vials of pembrolizumab are reimbursed by NHI (Taiwan). If a weight-based dosage method were adopted and vials of both strengths were reimbursed, pembrolizumab combination therapy as a first-line treatment for NSCLC would be more cost-effective for people with a body weight <75 kg.

The other factor that influences study outcomes is the second-line treatment cost. Our study's second-line treatment course length was calculated on the basis of the KEYNOTE-189 survival curve. The second-line treatment fee was also changed if the patients received third-line treatment. In such cases, we could not determine when the patients began the third-line treatment course. Therefore, we referred to data from the KEYNOTE-010 trial, which compared pembrolizumab and docetaxel as second-line therapies for patients with NSCLC [49,51]. We used data related to PFS and differences in OS to calculate the lengths of the second-line and third-line courses. This method prevents patients from being charged for costs related to immunotherapy after starting courses of third-line treatment. The adjusted costs of subsequent one-time treatments for the pembrolizumab combination and chemotherapy alone groups were NT$153,249 and NT$426,413, respectively. The ICER was NT$2,699,618/QALY, indicating that pembrolizumab therapy is still cost-effective.

In Taiwan, the NHI reimbursement criteria restrict the reimbursement of pembrolizumab as a first-line therapy for NSCLC for patients who are unfit for chemotherapy and with a PD-L1 TPS of ≥50%. According to the subgroup analysis in this study, patients were divided into PD-L1 TPS ≥50%, 1%–49%, and <1% groups, and the ICERs for these groups were NT$2,258,358/QALY, NT$2,624,878/QALY, and NT$2,501,406/QALY, respectively. Although the ICERs of the PD-L1 TPS 1%–49% and <1% groups were higher than that of the PD-L1 TPS ≥50% group, pembrolizumab combination therapy was still determined as cost-effective for all three groups.

However, there are few limitations to our study that deserve consideration. First, the KEYNOTE-189 trial permitted patients with verified disease progression in the chemotherapy alone group to cross over to pembrolizumab monotherapy. This may have reduced the difference in OS between the two groups. However, in the clinical practice in Taiwan, we can use pembrolizumab after failure to first-line chemotherapy. It reflects current treatment algorithms in Taiwan and we include pembrolizumab as one of the second-line treatment option in our model, so the impact of crossover to OS should be limited. Besides, extrapolating the overall survival data from KEYNOTE-189 study may not reflect the real-world condition. Therefore, we performed one-way deterministic sensitivity analyses and probabilistic sensitivity analysis to mitigate the impact of extrapolation. Second, we only selected severe AEs with high incidence to calculate the cost of AE management, which may have caused the costs of AE management to be underestimated. However, the disease management cost in our study was derived from the direct medical costs in the literature, which included the cost of outpatient treatment for AEs [37]. A sensitivity test was performed by adjusting the variation range to ±50% and the results remained similar. Therefore, the cost of AE management's effect on our study was limited. Finally, no data directly comparing pembrolizumab combination therapy with pembrolizumab alone were available; therefore, we could not determine which regimen is more cost-effective [25,52,53].

5. Conclusion

This pharmacoeconomic study from the perspective of NHI (Taiwan) demonstrated that the ICER of pembrolizumab plus platinum-based chemotherapy for metastatic nonsquamous NSCLC compared with standard chemotherapy is less than the WTP threshold. Pembrolizumab combination therapy is especially cost-effective for patients with PD-L1 TPS ≥50%.

Conflict of interest

The authors did not have any conflict of interest.

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