International Journal of Clinical Pharmacy
https://doi.org/10.1007/s11096-024-01826-7

RESEARCH ARTICLE

Cost-effectiveness analysis of first line pembrolizumab monotherapy for high programmed cell death ligand 1 expressed, advanced non-small cell lung cancer in Japan

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Received: 15 April 2024 / Accepted: 18 October 2024

Abstract

Background Pembrolizumab monotherapy significantly extends progression-free and overall survival compared to platinum-based chemotherapy for advanced non-small cell lung cancer (NSCLC), but also has a significant impact on medical costs.

Aim To clarify the health economic evidence for selecting the first-line treatment for patients with stage IV advanced NSCLC with a programmed cell death ligand 1 tumor proportion score of 50% or greater in Japan, we assessed the cost-effectiveness of pembrolizumab monotherapy compared with that of platinum-based chemotherapy.

Method Using a Markov model, the study simulated three health states for patients, based on clinical data and utility values from KEYNOTE-024. Transition probabilities were estimated exponentially. Direct medical costs were calculated according to the 2022 National Health Insurance Medical Fee Points and Drug Price Standards. The outcomes measured included life years, quality-adjusted life years, and incremental cost-effectiveness ratio, with sensitivity analysis performed to evaluate the effect of uncertainties.

Results Pembrolizumab led to an additional 1.58 life years and 1.23 quality-adjusted life years at an additional cost of 7,009,888 Japanese yen (48,448 U.S. dollars [USD]), resulting in incremental cost-effectiveness ratio of 4,436,638 Japanese yen (30,663 USD) per life year and 5,699,096 Japanese yen (39,388 USD) per quality-adjusted life year. Pembrolizumab was deemed cost-effective under a threshold of 7.5 million Japanese yen (51,835 USD) per quality-adjusted life year.

Conclusion Pembrolizumab monotherapy is a cost-effective option for the first-line treatment of advanced NSCLC with high programmed cell death ligand 1 expression in Japan, providing valuable health economic evidence for treatment selection.

Keywords Cost-benefit analysis · Lung neoplasms · Markov chains · Pembrolizumab · Quality-adjusted life years

Impact statements

- Pembrolizumab monotherapy is a cost-effective and efficient therapy with an incremental cost-effectiveness ratio of 5,699,096 Japanese yen (39,388 USD) per quality-adjusted life year.
- Patients who can tolerate platinum-based chemotherapy after pembrolizumab monotherapy can continue to receive efficient treatment with an incremental cost-effectiveness ratio of 7,379,654 Japanese yen (51,003 USD) per quality-adjusted life year.
- The information from this study is important health economic evidence for determining the first-line treatment for patients with advanced non-small cell lung cancer with high programmed cell death ligand 1 expression.

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Published online: 20 November 2024

Introduction

Lung cancer is the most common cause of cancer-related death worldwide [1]. The Japanese mortality rate of lung cancer is high in both males and females and increases with age [2]. Lung cancer is classified into small-cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC accounts for approximately 80% of all lung cancers and is often diagnosed at an advanced stage.

Cytotoxic chemotherapy has been used to treat stage IV NSCLC for several years. In the 2000s, molecular-targeted drugs and immune checkpoint inhibitors (ICI) emerged. Thus, the treatment paradigm for advanced NSCLC has changed dramatically. In 2015, pembrolizumab was approved by the U.S. Food and Drug Administration for the treatment of advanced NSCLC with programmed cell death ligand 1 (PD-L1) positivity. In Japan, pembrolizumab was approved in December 2016 for the treatment of PD-L1-positive, unresectable, advanced, or recurrent NSCLC. It is one of the first-line treatments for patients with advanced NSCLC who have a PD-L1 tumor proportion score (TPS) of 50% or greater and without epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations.

The efficacy and safety profile of pembrolizumab were reported in KEYNOTE-024, an international randomized phase III clinical trial, and compared with platinum-based chemotherapy in patients with untreated PD-L1 high-expressing NSCLC. The median progression-free survival (PFS) was reported at 10.3 months for pembrolizumab monotherapy and 6.0 months for chemotherapy (hazard ratio [HR] = 0.50, 95% confidence interval [CI]: 0.37–0.68) [3]. The median overall survival (OS) in pembrolizumab monotherapy was significantly longer than that of chemotherapy (26.3 vs. 13.4 months, HR = 0.62, 95%CI: 0.48–0.81). Additionally, the 5-year OS rate has been reported to be 31.9% for pembrolizumab monotherapy and 16.3% for chemotherapy [4]. Therefore, pembrolizumab monotherapy is highly recommended in the National Comprehensive Cancer Network practice guideline as a first line treatment for patients with advanced NSCLC with high PD-L1 expression [5].

In Japan, National Medical Expenditure reached approximately 45 trillion yen in 2021, with malignancies accounting for nearly 4.8 trillion yen, and continues to increase [6]. Anticancer drugs require repeated administration to achieve outcomes, resulting in high medical costs. Pembrolizumab monotherapy notably influences national medical costs. While cost-effectiveness analyses in other countries have shown pembrolizumab to be cost-effective in Switzerland, France, and the US, it was found not to be so in China and the UK [7–11].

Pembrolizumab monotherapy is highly recommended in the Japanese practice guideline as a first line treatment for patients with advanced NSCLC with high PD-L1 expression. However, despite the high cost of pembrolizumab, Japan lacks studies evaluating its cost, survival, and utility values as a first-line treatment for advanced NSCLC with a PD-L1 TPS of 50% or higher. Therefore, decision making for the treatment of advanced NSCLC should include not only clinical efficacy but also cost-effectiveness.

Aim

To clarify the health economic evidence for selecting the first-line treatment for patients with stage IV advanced NSCLC with a PD-L1 TPS of 50% or greater in Japan, we assessed the cost-effectiveness of pembrolizumab monotherapy compared with that of platinum-based chemotherapy.

Ethics approval

The Clinical Trials Act (Ministry of Health, Labour and Welfare, Japan) and Ethical Guidelines for Medical and Biological Research Involving Human Subjects (Ministry of Health, Labour and Welfare, Japan) do not require ethical review for publicly available information. In addition, this study did not require personal information as defined by the Act on the Protection of Personal Information.

Method

Patient population

The study population comprised KEYNOTE-024 participants [3]. The inclusion criteria were as follows: greater than 18 years old, stage IV NSCLC without EGFR mutations or ALK translocations, no previous systemic treatments for metastatic disease, Eastern Cooperative Oncology Group performance status score of 0 or 1, at least one measurable lesion in line with the Response Evaluation Criteria in Solid Tumors, and a PD-L1 TPS of 50% or greater.

As first-line treatment, patients in the pembrolizumab group received a 200 mg intravenous dose of pembrolizumab once every 3 weeks for up to 35 cycles. In clinical practice, pembrolizumab can be administered at 400 mg every 6 weeks. However, this regimen was not included in the protocol of KEYNOTE-024; therefore, it was not included as a dosage in this study. The chemotherapy group received platinum-based chemotherapy. Chemotherapy regimens differed between squamous and non-squamous cell carcinoma, with 17.9% and 82.1% of patients being treated for these conditions, respectively. As carboplatin is routinely used in Japan, patients with squamous cell carcinoma received a

combination of carboplatin (area under the curve [AUC], 6) and paclitaxel (200 mg/m²) every 3 weeks for 6 cycles. Furthermore, patients with non-squamous cell carcinoma received a combination of carboplatin (AUC, 5–6) and pemetrexed (500 mg/m²) every 3 weeks for 4 cycles. After 4 cycles, pemetrexed monotherapy was administered as maintenance therapy.

As second-line treatment, patients in the pembrolizumab group received docetaxel (60 mg/m²) every 3 weeks. However, crossover to platinum-based chemotherapy could be permitted as subsequent therapy. In the 5-year OS update of KEYNOTE-024, 57 of 154 patients (37%) in the pembrolizumab group were selected to receive platinum-based chemotherapy with or without bevacizumab as subsequent therapy. Thus, crossover was observed in 37% of the patients in the pembrolizumab group [4]. The regimen for platinum-based chemotherapy was carboplatin/paclitaxel for squamous cell carcinoma and carboplatin/pemetrexed for non-squamous cell carcinoma, followed by pemetrexed maintenance therapy. The treatment schedule was the same as that for the first-line treatment. Patients in the chemotherapy group received docetaxel every 3 weeks as second-line treatment. However, crossover to pembrolizumab was permitted, and observed in 43.7% of patients [3]. The treatment schedule was the same as that for the first-line treatment.

Model structure

A Markov model was constructed using TreeAge Pro 2023 software to simulate the clinical course of pembrolizumab monotherapy or platinum-based chemotherapy [12]. Figure 1 presents a Markov model showing the patient's health state and transition during each cycle.

The Markov model consists of three health states: progression-free (PF), progressive disease (PD), and death. Each health state is associated with a corresponding cost and transition probability of moving from one state to another after one cycle. A three-state Markov model was simulated for both treatment groups. All patients were initially in the PF state and received either pembrolizumab monotherapy or platinum-based chemotherapy as first-line treatment. Once progression was observed, patients moved from the PF state to the PD state. PD refers to a condition in which the disease has advanced despite treatment, leading patients to receive the second-line treatment to manage their condition. This treatment was continued from progression to death. If patients progressed after second-line treatment, they received terminal care for 1 month and moved to the death state. The length of one cycle in the model was 3 weeks. The time horizon was set at 20 years, or until 99% of the patients died. The validity of the developed Markov model and treatment schedule was confirmed by lung cancer specialists.

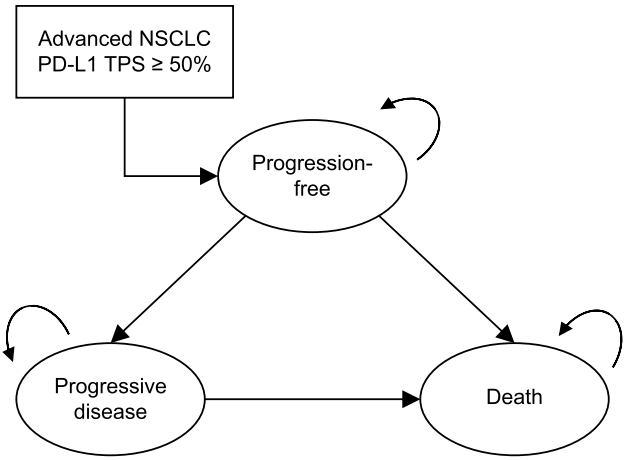

Fig. 1 Markov model structure and transitions. NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score

We measured the expected total costs, expected life-years (LYs), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER) and compared the ICER with the threshold to determine whether pembrolizumab monotherapy is efficient. The threshold was defined as 7.5 million Japanese yen (JPY) based on a discussion by the Central Social Insurance Medical Council [13]. As the analysis lasted longer than 1 year, the discount rate was set at 2% [14]. Costs and ICER were expressed in JPY and U.S. dollars (USD). The exchange rate at the time of analysis was 144.69 JPY per 1 USD in December 2023.

Transition probabilities

Survival data for OS and PFS were available from KEYNOTE-024 and the 5-year OS update of KEYNOTE-024 [3, 4]. The transition probabilities were assumed to follow an exponential distribution. The transition probability at time t is expressed by Eq. 1; γ is the rate of transition to another state per unit time, and was determined as follows: the rate of progression from the PF state to the PD state was calculated from the median PFS in both groups [3]. The mortality of the population directly transitioning from the PF state to the death state was calculated from treatment-related deaths in both groups: 2 of 154 patients in the pembrolizumab group and 4 of 151 patients in the chemotherapy group [4]. The rate from the PD state to the death state was calculated in accordance with the OS data. In addition, these rates were corrected using TreeAgePro 2023 with the PFS and OS data as target points (Supplementary Information Table 1), and the corrected rates were substituted into the transition rate matrix (Eq. 2) to obtain the transition probabilities. The key parameters of the base-case analysis are summarized in Table 1.

$$p(t) = 1 - e^{-\gamma t} \quad (1)$$

$$G = \begin{pmatrix} -(\gamma_{PFtoPD} + \gamma_{PFtodeath}) & \gamma_{PFtoPD} & \gamma_{PFtodeath} \\ 0 & -\gamma_{PDtodeath} & \gamma_{PDtodeath} \\ 0 & 0 & 1 \end{pmatrix} \quad (2)$$

Treatment-related adverse events of grade 3 or higher, as reported by the 5-year OS update of KEYNOTE-024, were included in the model [4]. These were observed in 31.2% of patients in the pembrolizumab group and 53.3% in the chemotherapy group.

Measurement of costs

We estimated only the direct medical costs. The analysis was conducted from the perspective of public healthcare payers in Japan. The costs of drugs, outpatient expenses, examinations, diagnostic imaging, and terminal care were included as direct medical costs. The prices were in accordance with the National Health Insurance price and Medical Fee Point and the Drug Price Tariff in 2022 [15, 16]. The cost of drugs was calculated based on the price of drugs with brand names. To estimate the cost of anticancer agents, we assumed that the base-case patients were 65 years old, had

Table 1 Key parameters of base-case analysis

Parameters	Base case	Range	Distribution	Source
Clinical parameters				
Pembrolizumab, PF to PD, rate	0.620	0.496–0.744	Exponential	[3, 4]
Pembrolizumab, PF to death, rate	0.002	0–0.002	Exponential	[3, 4]
Pembrolizumab, PD to death, rate	0.754	0.603–0.904	Exponential	[3, 4]
Chemotherapy, PF to PD, rate	1.327	1.061–1.592	Exponential	[3, 4]
Chemotherapy, PF to death, rate	0.004	0–0.004	Exponential	[3, 4]
Chemotherapy, PD to death, rate	1.675	1.34–2.01	Exponential	[3, 4]
Second line platinum-based chemotherapy rate	0.370	0–1	Beta	[4]
Cross over rate	0.437	0.349–0.642	–	[3]
Cost (JPY)				
Cost of drug per cycle				
Pembrolizumab	428,996	–	Gamma	[16]
CBDCA/PEM	265,667	–	Gamma	[16]
PEM maintenance	228,087	–	Gamma	[16]
CBDCA/PTX	61,622	–	Gamma	[16]
DTX	38,727	–	Gamma	[16]
Cost of outpatient expenses per cycle				
Pembrolizumab	6,190	–	Gamma	[15, 16]
CBDCA/PEM	8,730	–	Gamma	[15, 16]
PEM maintenance	8,240	–	Gamma	[15, 16]
CBDCA/PTX	6,680	–	Gamma	[15, 16]
DTX	6,680	–	Gamma	[15, 16]
Cost of examinations per cycle	9,978	–	Gamma	[15]
Cost of free T3, free T4, and TSH per cycle	1,745	–	Gamma	[15]
Cost of diagnostic imaging per cycle	6,798	–	Gamma	[15]
PD-L1 testing cost (one time)	28,300	22,640–33,960	Gamma	[15]
Initial cost of CBDCA/PEM (one time)	2,936	2,232–3,348	Gamma	[15, 16]
Terminal care cost (one time)	1,120,000	896,000–1,344,000	Gamma	[17]
Utility values				
Pembrolizumab, PF	0.808	0.793–0.823	Beta	[18]
Chemotherapy, PF	0.757	0.738–0.775	Beta	[18]
Pembrolizumab, PD	0.737	0.703–0.771	Beta	[18]
Chemotherapy, PD	0.687	0.646–0.727	Beta	[18]
Discount rate (%)	2	0–4	–	[14]

CBDCA, carboplatin; DTX, docetaxel; JPY, Japanese yen; OS, overall survival; PD, Progressive disease; PD-L1, programmed cell death ligand 1; PEM, pemetrexed; PF, Progression-free; PFS, progression-free survival; PTX, paclitaxel; SD, standard deviation; TSH, thyrotropin

a body surface area of 1.65 m^2, and had normal renal function. Outpatient expenses were calculated, including outpatient treatment fees, prescription fees, medical fees related to outpatient chemotherapy, and medical fees incurred by out-of-hospital pharmacies. Blood counts and biochemical examinations were performed at the expense of the examinations. The patients in both groups underwent additional companion diagnostic examinations to determine PD-L1 expression. Furthermore, the costs of testing free T3, free T4, and thyrotropin (TSH) to identify immune-mediated adverse events were calculated. The cost of diagnostic imaging was calculated for chest radiography, computed tomography (CT), and magnetic resonance imaging (MRI). The frequency of these calculations was assumed to be every 3 weeks for outpatient costs, blood count tests, and biochemical examinations, and every 6 weeks for free T3, free T4, and TSH. Chest radiography and CT were performed every 12 weeks, and MRI was performed every 52 weeks. The cost of terminal care included those required for approximately 1 month until death. A one-time cost was set using data compiled by the Ministry of Finance and Ministry of Health, Labour and Welfare in 2007 [17]. Table 1 lists the costs used in the base-case analysis. The details of the unit price of each item and the frequency of calculation are shown in the Supplementary Information (see Electronic Supplementary Material Table 2).

Utilities

As the efficacy of pembrolizumab has not been documented, we derived the utility values from the EuroQOL 5 dimension 3-level in KEYNOTE-024 reported at the conference [18]. Utility values were set for health states ranging from 0 (death) to 1 (perfect state). The utility values of the PF status in the pembrolizumab and chemotherapy groups were 0.808 and 0.757, respectively, while those for the PD state in the pembrolizumab and chemotherapy groups were 0.737 and 0.687, respectively. Furthermore, the disutility values associated with adverse events were calculated by subtracting 0.09 based on a previous study [19]. Table 1 shows the utility values for each health status.

Sensitivity analysis

One-way sensitivity analysis was performed to identify the variables that influenced the model results. The results are presented as a tornado diagram. The rate, a parameter for calculating transition probability, varied from low-high ranges of ± 20% of the base-case. The values of cost and utilities were assumed to be uniformly distributed with low-high ranges of ± 20% of the base-case. The discount rate varied from 0 to 4% [14].

Using Monte Carlo simulations, a probabilistic sensitivity analysis was performed to explore the factors that can influence the ICER. Monte Carlo simulations were simultaneously varied for all parameters according to the specified distributions. The exponential distribution was used for the rate parameters which estimated the transition probability. The gamma distribution was used for cost parameters, whereas the beta distribution was used for utility parameters. The Monte Carlo simulation was run 10,000 times, and the results were presented as a cost-effectiveness acceptability curve.

In the scenario analysis, we evaluated the effects of the following assumptions on the results. In the first scenario, we assumed that the probability of selecting platinum-based chemotherapy as subsequent therapy in the pembrolizumab group was 100%. In the second scenario, we assumed that the utility values for both groups were the same for each health state. In the third scenario, we assumed that the cost of anticancer drugs except pembrolizumab was changed to the cost of generic drugs (see Electronic Supplementary Material Table 3).

Model simulations and sensitivity analyses were performed using TreeAgePro2023 (TreeAge Software Inc., Williamstown, MA, USA).

Results

Base-case results

Table 2 shows the results of the base-case analysis. The pembrolizumab group gained an extra 1.58 LYs over the chemotherapy group (2.89 vs. 1.31 LYs) and had an additional 1.23 QALYs compared to chemotherapy (2.16 vs. 0.93 QALYs). The expected total cost in the pembrolizumab group was 7,009,888 JPY (48,448 USD), which is higher than that of the chemotherapy group (11,684,001 JPY vs. 4,674,113 JPY [80,752 USD vs. 32,304 USD]). The pembrolizumab group had an ICER of 4,436,638 JPY per LY (30,663 USD/LY) and 5,699,096 JPY per QALY (39,388 USD/QALY).

Sensitivity analysis

Figure 2 shows the results of the one-way sensitivity analysis. The probability of selecting platinum-based chemotherapy as subsequent therapy in the pembrolizumab group was the most sensitive parameter affecting the ICER. Other sensitive parameters included the cost of pembrolizumab, crossover rate, and the rate from the PD state to death state in pembrolizumab group.

The results of the probabilistic sensitivity analysis, the average ICER was 5,676,889 JPY per QALY (39,234 USD/QALY), with an average QALY gain of 1.22 and a mean

Table 2 Results of the cost-effectiveness analysis

	Pembrolizumab	Chemotherapy	Difference
Base-case analysis			
Effectiveness			
LYs	2.89	1.31	1.58
QALYs	2.16	0.93	1.23
Cost (JPY)			
Expected cost	11,684,001	4,674,113	7,009,888
ICER (JPY)			
Per LY			4,436,638
Per QALY			5,699,096
Probabilistic sensitivity analysis			
Effectiveness			
Mean QALYs	2.16	0.94	1.22
Cost (JPY)			
Mean cost	11,664,419	4,738,614	6,925,805
ICER (JPY)			
Per QALY			5,676,889

ICER, incremental cost-effectiveness ratio; JPY, Japanese yen; LY, life year; LYs, life years; QALY, quality-adjusted life year; QALYs, quality-adjusted life years

incremental cost of 6,925,805 JPY (47,867 USD). Figure 3 presents the results of the probabilistic sensitivity analysis using the cost-effectiveness acceptability curve. The probability of the pembrolizumab group being more cost-effective than the chemotherapy group was 99.58% at a threshold of 7.5 million JPY per QALY (51,835 USD/QALY).

Table 3 presents the results of the scenario analysis. When the probability of selecting platinum-based chemotherapy as subsequent therapy in the pembrolizumab group was 100%, the average ICER was 7,379,654 JPY per QALY (51,003 USD/QALY), which was higher than in the base-case. The acceptability of cost-effectiveness of pembrolizumab treatment was 57.74%. When the utility values of both groups were equal, the average ICER was 6,919,182 JPY per QALY (47,821 USD/QALY), which was higher than in the base-case. The acceptability of cost-effectiveness of pembrolizumab treatment was 77.36%. When the cost of anticancer drugs other than pembrolizumab was changed to the cost of their corresponding generic drugs, the average ICER was 5,972,304 JPY per QALY (41,277 USD/QALY), which was higher than the base-case. The probability of being cost-effective in the pembrolizumab group was 98.66%.

Discussion

In this study, we demonstrated, to our knowledge, the first evidence of the cost-effectiveness of pembrolizumab monotherapy compared to platinum-based chemotherapy for patients with NSCLC with a PD-L1 TPS of 50% or higher in Japan. Our results provide compelling health economic justification for recommending pembrolizumab as the primary treatment for this patient group.

The cost-effectiveness of pembrolizumab monotherapy was verified after assuming the actual clinical practice and cost estimation in Japan. First, we assumed the subsequent therapy after pembrolizumab monotherapy according to the clinical practice guideline. In clinical practice, cytotoxic therapy regimens are recommended as subsequent therapies, and platinum-based chemotherapy is mostly selected. Since this was parameters that affected ICER, we investigated the impact on ICER in the scenario analysis. Our findings revealed an ICER of 7,379,654 JPY per QALY (51,003 USD/QALY), which increased in comparison with the base-case analysis. The probability of being cost-effective in the pembrolizumab group at the Japanese threshold was 57.74%. Therefore, pembrolizumab monotherapy can be considered an efficient treatment, even if chemotherapy is selected as post-treatment.

Second, the total cost for patients with NSCLC during the first 1–2 years was reported as 16.04 million JPY (110,857 USD) (interquartile range, 8.98–26.70 million JPY [62,063–184,532 USD]) [20]. The incremental cost in our study was below this range, which was considered acceptable. The additional cost of switching from chemotherapy to pembrolizumab monotherapy was expensive. We demonstrated that pembrolizumab monotherapy can be received within the range of conventional medical costs.

Furthermore, when the cost of anticancer drugs other than pembrolizumab was changed to the cost of the generic drugs in the scenario analysis, the ICER was 5,972,304 JPY per QALY (41,277 USD/QALY), and the acceptability of cost-effectiveness of pembrolizumab treatment was 98.66%. In Japan, the target is to increase the use of generic drugs to 80% or more by 2023. This analysis included the actual use of generic drugs in Japan, and demonstrated that pembrolizumab monotherapy was an efficient treatment.

The LYs and QALYs in this study is similar to that reported in the UK [11], which could be attributed to the fact that both studies selected a Markov model and the transition probability followed an exponential distribution. The technology appraisal guidance from the UK National Institute for Health and Care Excellence (NICE), shares similarities with Japanese health insurance system, highlights the uncertainties regarding the target point of extrapolation of OS data and the duration of response following the discontinuation

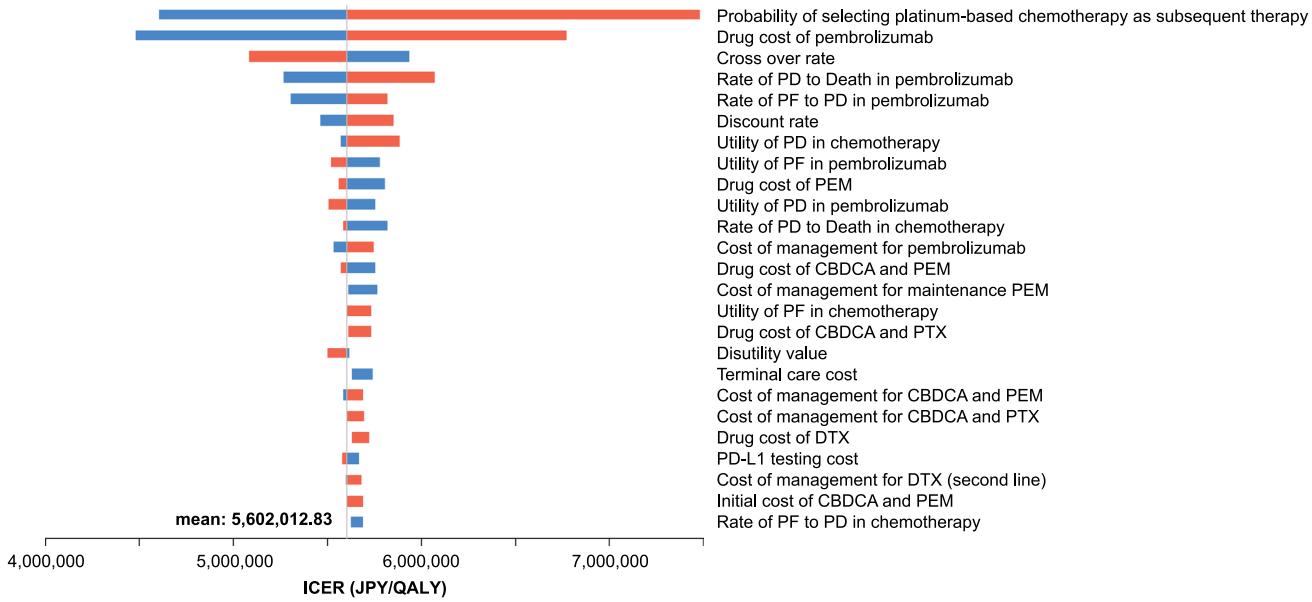

Fig. 2 Tornado diagram summarizing one-way sensitivity analysis comparing pembrolizumab and chemotherapy groups to identify the model variables. CBDCA, carboplatin; DTX, docetaxel; ICER, incremental cost-effectiveness ratio; JPY, Japanese yen; PD, progressive disease; PD-L1, programmed cell death ligand 1; PEM, pemetrexed; PF, progression-free; PTX, paclitaxel, QALYs, quality-adjusted life years

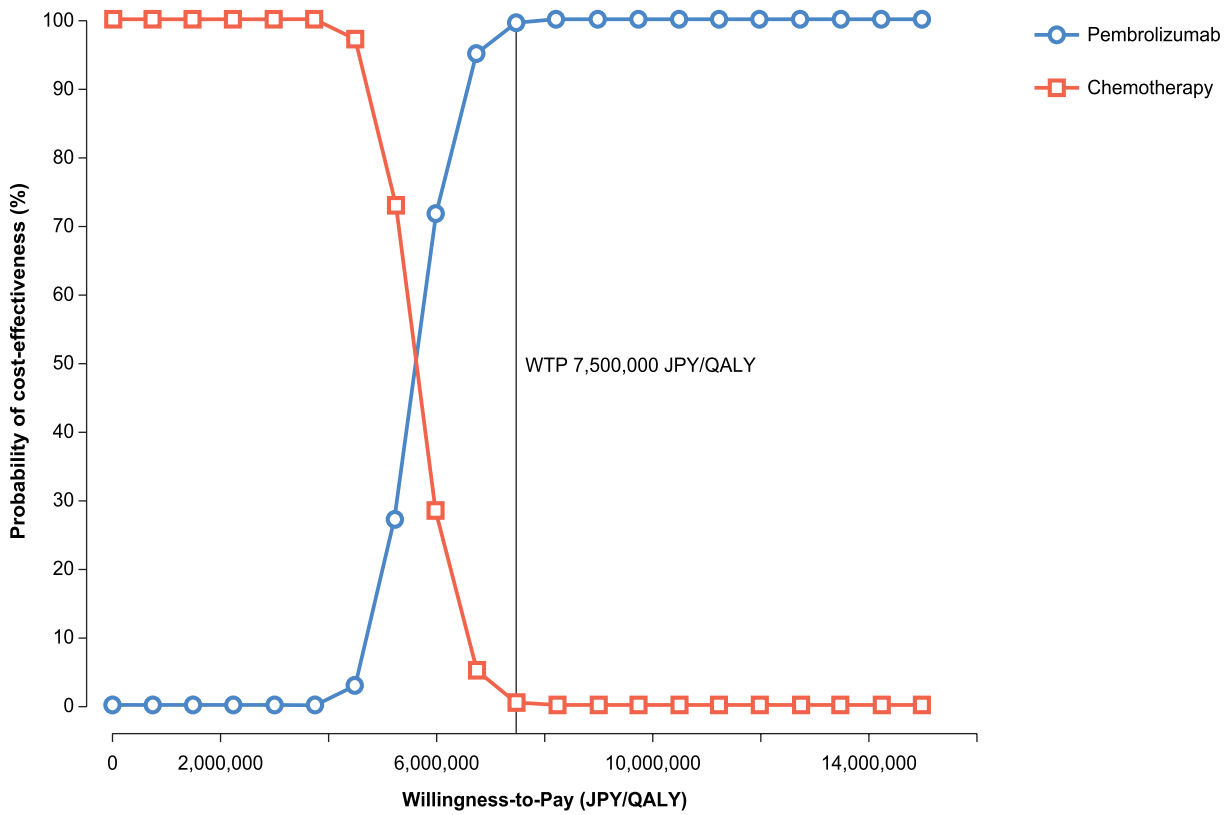

Fig. 3 Cost-effectiveness acceptability curves. JPY, Japanese yen; QALYs, quality-adjusted life years; WTP, willingness-to-pay

Table 3 Results of the scenario analysis

	Pembrolizumab	Chemotherapy	Difference
Case 1. The probability of selecting platinum-based chemotherapy as the subsequent therapy in the pembrolizumab group was 100%			
Effectiveness			
Mean LYs	2.89	1.32	1.57
Mean QALYs	2.17	0.94	1.23
Cost (JPY)			
Mean cost	13,813,620	4,736,646	9,076,974
ICER (JPY)			
Per QALY			7,379,654
Cost effectiveness acceptability (%)	57.74	42.26	
Case 2. Same utility values			
Effectiveness			
Mean LYs	2.89	1.32	1.57
Mean QALYs	1.82	0.82	1.00
Cost (JPY)			
Mean cost	11,655,231	4,736,049	6,919,182
ICER (JPY)			
Per QALY			6,919,182
Cost effectiveness acceptability (%)	77.36	22.64	
Case 3. Changing the cost of anti-cancer drugs to the cost of their respective generics			
Effectiveness			
Mean LYs	2.89	1.32	1.57
Mean QALYs	2.17	0.94	1.23
Cost (JPY)			
Mean cost	10,355,597	3,009,663	7,345,934
ICER (JPY)			
Per QALY			5,972,304
Cost effectiveness acceptability (%)	98.66	1.34	

ICER, incremental cost-effectiveness ratio; JPY, Japanese yen; LYs, life years; QALY, quality-adjusted life year; QALYs, quality-adjusted life years

of pembrolizumab [21]. In this study, the one-way sensitivity analysis identified the rate from the PD state to the death state in the pembrolizumab group as a parameter with uncertainty; however, its impact on the ICER was minimal. The ICER in this study was comparable to that of NICE (30,244 GBP/QALY), with minimal impact from the extrapolated transition probabilities calculated from the exponential function on the model. Therefore, the results of this study were similar to those of other studies.

The drug cost of pembrolizumab was extracted using a one-way sensitivity analysis. Previous studies have also reported that the drug cost of pembrolizumab is expensive and is an influential parameter in the ICER [10, 11]. However, the ICER was within the threshold when the drug cost of pembrolizumab was changed to a low-high range of 20% of the base-case in this study. The ICER in this study was smaller than that in the UK study (5,699,096 JPY/QALY [31,160 GBP/QALY] vs. 86,913 GBP/QALY, [exchange rate 1 GBP = 182.90 JPY, 2023/12]) [11]. Hence, this study demonstrated that the cost of pembrolizumab does not have a significant impact on the ICER due to the lower cost of pembrolizumab than that in other countries.

Direct costs were estimated according to the KEYNOTE-024 treatment schedule, which involved cisplatin- or carboplatin-based regimens. We utilized a carboplatin-based regimen for chemotherapy cost estimation. Carboplatin was selected based on the advice of a clinical specialist, such as toxicity, hydration status, and outpatient feasibility. We believe that our estimation was the optimal setting to reflect the practical clinical scenarios in Japan.

This study has several limitations. First, terminal care costs were established as a one-time expense, which was cited from the 2007 report [17]. Awano et al. reported that the terminal care costs for NSCLC in the final 3 months before death ranged from 1.79 to 2.18 million JPY per month, covering chemotherapy and immunotherapy [22].

The terminal costs in this study were below the estimates by Awano et al., and considering the disease progression, it was reasonable to exclude chemotherapy and immunotherapy costs. Identifying the actual costs is challenging owing to the diverse drugs for lung cancer symptoms. Future cost estimations should utilize real world and receipt data.

Second, the rate was adjusted using the 6-month, 3-year, 4-year, and 5-year OS rate from KEYNOTE-024 to reflect the long-term survival of pembrolizumab monotherapy [3, 4]. Our 5-year OS rates were 14.4% and 0.5% for the pembrolizumab and chemotherapy groups, respectively. Compared to previous report, our 5-year OS rate was lower in both groups, which is attributed to the fact that the transition probability is estimated to follow an exponential distribution. ICI therapy is deemed effective during treatment and even after discontinuation. Since the exponential function indicates that the events occurred at a constant hazard rate, approximating the characteristics of the tail of the Kaplan–Meier curve proves difficult. Thus, transition probability had a large impact on the ICER and was a limitation in estimating long-term survival despite using the latest data. Therefore, we consider that correction using real-world data and analysis by the partitioned survival model are necessary to minimize the impact of survival function on the ICER.

The third limitation was relying on pembrolizumab utility values sourced from conference presentations lacking documented evidence. Existing literature suggests that the utility values in first-line treatment for patients with NSCLC were 0.72 for chemotherapy (cisplatin/pemetrexed) and 0.65 for erlotinib [23]. In another study, analysis was performed assuming that the utility values for the chemotherapy and pembrolizumab groups were equated [10]. Thus, we conducted a scenario analysis with identical utility values for both groups, resulting in 1.00 incremental QALYs, which is lower than the base-case. This suggests that the pembrolizumab utility values in our analysis may be higher than those in previous studies. Despite potential overestimation of patient QOL, the scenario analysis ICER was 6,919,182 JPY per QALY (47,821 USD/QALY), which is below the acceptability threshold. Therefore, adjusting utility values in this scenario did not present significant issues.

Fourth, the settings of the model were limited, particularly in the choice of the comparator. As a rule, the comparator is widely used and is expected to replace existing treatments. At the time of study analysis, platinum-based chemotherapy was used as the comparator. Chemotherapy was also used as the comparator in the KEYNOTE-024 study. The other first line treatment options include atezolizumab monotherapy and platinum-based chemotherapy with PD-1/PD-L1 inhibitors. However, no clinical studies have directly compared pembrolizumab monotherapy with these therapies, and it remains unclear whether the addition of a PD-1/PD-L1 inhibitor to platinum-based combination therapy is superior to pembrolizumab or atezolizumab monotherapy. Consequently, we selected chemotherapy as the model comparator.

ICIs other than pembrolizumab were not considered as subsequent treatment in the chemotherapy group. In the 5-year OS update of KEYNOTE-024, excluding crossovers to pembrolizumab, 1.3% of patients in the chemotherapy group crossed over to atezolizumab and 6.6% to nivolumab [4]. Failing to account for this may have reduced the expected cost of subsequent treatment in the chemotherapy group. Therefore, the administration of atezolizumab or nivolumab as a subsequent treatment was less frequent in the overall chemotherapy group, but it should have been included in the analysis.

Finally, analyses using data from clinical trials, such as this study may have gaps between the eligibility criteria for patients in clinical trials and those for actual clinical practice. The difference in eligibility criteria for patients include being old age, decreased PS, increased likelihood of adverse events, and decreased survival. Therefore, correcting the setting of the model using clinical trial data with real-world data is warranted.

Conclusion

This study demonstrated the cost-effectiveness of pembrolizumab monotherapy over platinum-based chemotherapy as first-line treatment for NSCLC patients with a PD-L1 TPS of 50% or greater in Japan. The ICER was 5,699,096 JPY per QALY (39,388 USD/QALY), which was below the Japanese threshold of 7.5 million JPY per QALY (51,835 USD/QALY). This study provides evidence that supports the recommendation of pembrolizumab monotherapy on both medical and economic grounds. Cost-effectiveness, including resource allocation, is crucial when selecting expensive drugs, such as pembrolizumab.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11096-024-01826-7.

Funding No specific funding was received.

Conflicts of interest The authors have no conflicts of interest to declare.

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