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Cost-effectiveness analysis of pembrolizumab versus chemotherapy as first-line treatment in locally advanced or metastatic non-small cell lung cancer with PD-L1 tumor proportion score 1% or greater

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ABSTRACT

Objective: The purpose of this study was to estimate the cost-effectiveness analysis of pembrolizumab versus chemotherapy as first-line treatment in locally advance or metastatic non-small cell lung cancer (NSCLC) with programmed death ligand 1 (PD-L1) tumor proportion score (TPS) 1% or greater from the United States (US) payer perspective.

Materials and Methods: This Markov structure was developed to estimate cost and effectiveness of pembrolizumab vs chemotherapy in the first-line treatment of locally advance or metastatic NSCLC based on the data from KEYNOTE-042. Cost and health outcomes were estimated at a willingness-to-pay (WTP) threshold of $150,000 per quality adjusted life year (QALY) in three PD-L1 TPS populations (≥50%, ≥20% and ≥1%). One-way, two-way and probabilistic sensitivity analysis were to test the model stability. Subgroup analysis were performed in three PD-L1 TPS populations (≥50%, ≥20% and ≥1%).

Results: The incremental costs and QALYs that pembrolizumab yielded, compared with chemotherapy, were $86164.87 and 0.63, $74562.25 and 0.46 and $70886.65 and 0.39 for the populations with a PD-L1 TPS ≥ 50%, TPS ≥ 20% and TPS ≥ 1%, leading an incremental cost-effective ratio (ICER) of $136,228.82, $160,625.98 and $179,530.17 per QALY, respectively.

Conclusion: First-line treatment with pembrolizumab is a cost-effective strategy compared with platinum-based chemotherapy when the value of WTP was $150,000 per QALY in locally advanced or metastatic NSCLC patients with PD-L1 TPS ≥ 50% and without epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations, but not in the TPS ≥ 20% and 1% populations.

1. Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death worldwide, with 2.1 million new lung cancer cases and 1.8 million deaths per year [1–4]. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. Up to 61% of patients have advanced disease at the time of diagnosis, with a 5-year survival rate of 18% [5,6].

Platinum-based chemotherapy is the main treatment in lung cancer [7,8]. Recently, immune checkpoint inhibitors (ICIs) have changed the treatment paradigm of advanced NSCLC. Several agents blocking immune inhibitory pathways such as pembrolizumab and nivolumab, which directed against programmed cell death-1 (PD-1), atezolizumab, durvalumab and avelumab, targeting the programmed cell death receptor ligand-1 (PD-L1), or ipilimumab and tremelimumab, against cytotoxic T-lymphocyte antigen 4 (CTLA-4), have been already

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Table 1
Model parameters: baseline values, ranges, and distributions for sensitivity analysis.

Variable	Baseline value	Range		Reference	Distribution
		Minimum	Maximum		
Weibull survival model in Pembrolizumab group with TPS ≥ 50%					
PFS	Shape = 0.72847, Scale = 0.21200	–	–	(5)	–
OS	Shape = 0.788191, Scale = 0.088898	–	–	(5)	–
Weibull survival model in Chemotherapy group with TPS ≥ 50%					
PFS	Shape = 1.15331, Scale = 0.11631	–	–	(5)	–
OS	Shape = 0.946006, Scale = 0.086875	–	–	(5)	–
Weibull survival model in Pembrolizumab group with TPS ≥ 20%					
PFS	Shape = 0.78876, Scale = 0.20424	–	–	(5)	–
OS	Shape = 0.811564, Scale = 0.091588	–	–	(5)	–
Weibull survival model in Chemotherapy group with TPS ≥ 20%					
PFS	Shape = 1.190844, Scale = 0.10289	–	–	(5)	–
OS	Shape = 0.99432, Scale = 0.075732	–	–	(5)	–
Weibull survival model in Pembrolizumab group with TPS ≥ 1%					
PFS	Shape = 0.70146, Scale = 0.27077	–	–	(5)	–
OS	Shape = 0.809920, Scale = 0.098891	–	–	(5)	–
Weibull survival model in Chemotherapy group with TPS ≥ 1%					
PFS	Shape = 1.21192, Scale = 0.101104	–	–	(5)	–
OS	Shape = 0.979120, Scale = 0.082452	–	–	(5)	–
Rate of treatment discontinuation					
Pembrolizumab	0.38	–	–	(5)	–
Chemotherapy	0.448	–	–	(5)	–
Risk for main adverse events in chemotherapy group					
Risk of anemia	0.13	0.104	0.156	(5)	Beta
Risk of neutropenia	0.07	0.056	0.084	(5)	Beta
Risk of neutrophil count decreased	0.05	0.04	0.06	(5)	Beta
Risk of white blood cell count decreased	0.10	0.08	0.12	(5)	Beta
Pembrolizumab subsequent therapy proportion					
Crizotinib	0.03	–	–	(5)	–
Nivolumab	0.02	–	–	(5)	–
Chemotherapy subsequent therapy proportion					
Crizotinib	0.04	–	–	(5)	–
Nivolumab	0.13	–	–	(5)	–
Pembrolizumab	0.04	–	–	(5)	–
Utility					
Utility PFS pembrolizumab	0.691	0.5582	0.8292	(12, 13)	Beta
Utility PFS chemotherapy	0.653	0.5224	0.7863	(12, 20)	Beta
Utility PD	0.473	0.3784	0.5676	(12, 20)	Beta
Patients' weight, kg	70	–	–	(14, 16)	Beta
Body surface area, m^2	1.84	–	–	(14)	Beta
Drug cost, $/per cycle					
Pembrolizumab	19594.80	15,675.84	23,513.76	(15)	Gamma
Pemetrexed	12531.69	10,025.35	15,038.03	(15)	Gamma
Carboplatin	76.38	61.10	91.65	(14, 15)	Gamma
Paclitaxel	113.34	90.67	136.01	(15)	Gamma
Atezolizumab	18662.40	14,929.92	22,394.88	(15)	Gamma
Nivolumab	17107.65	13,686.12	20,529.18	(15)	Gamma
Ipilimumab	62424.60	49,939.68	74,909.52	(15)	Gamma
Crizotinib	93240.00	74,592.00	111,888.00	(15)	Gamma
Avelumab	17180.10	13,744.08	20,616.12	(15)	Gamma
Expenditures on main adverse events, $					
Anaemia	7969.56	6375.65	9536.47	(19)	Gamma
Neutropenia	32995	24746	41244	(20, 21)	Gamma
Neutrophil count decreased	32995	24746	41244	(20, 21)	Gamma
White blood cell count decreased	32995	24746	41244	(20, 21)	Gamma
Administration per cycle	139.61	111.69	167.53	(16)	Gamma
CT per cycle	231	208	254	(17)	Gamma
Laboratory per cycle	315	252	378	(18)	Gamma
Discount rate	0.03	–	–	(10)	–

Abbreviation: CTcompute tomography; NSCLCnon-small-cell lung cancer; PDprogressive disease; PFSprogression-free survival; TPStumor proportion score.

evaluated and some of them have already been approved for clinical use [9–13].

Pembrolizumab is a human immunoglobulin G4 monoclonal antibody that binds to the programmed death 1 receptor and restores T-cell immune activity. In the pivotal KEYNOTE-024 trial, pembrolizumab was indicated longer progression-free and overall survival (OS) and showed fewer treatment-related adverse events than platinum-based combination chemotherapy in patients with previously untreated advanced NSCLC and a PD-L1 tumor proportion score (TPS) of 50% or greater [9]. Subsequently, after the approval by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA), single-agent pembrolizumab became standard of care in advanced NSCLC patients with PD-L1 TPS ≥ 50%.

The KEYNOTE-042 study added another choice of first-line treatment for locally advanced or metastatic NSCLC and explored whether first-line pembrolizumab could be extended to patients with PD-L1 TPS ≥ 1%. The trial demonstrated that OS was significantly longer in the pembrolizumab group than in the chemotherapy group in all three PD-L1 TPS populations (≥1%, ≥20% and ≥50%). Not unexpectedly, the magnitude of OS benefit rose with increasing PD-L1 TPS (≥50%

hazard ratio 0·69, 95% CI 0·56–0·85, p = 0·0003; ≥20% 0·77, 0·64–0·92, p = 0·0020 and ≥1% 0·81, 0·71–0·930·69, 0·56–0·85, p = 0·0018) [14]. Single-agent pembrolizumab was subsequently approved as first-line treatment for patients with advanced NSCLC, PD-L1 TPS ≥ 1% by the US FDA in April 2019.

Due to the high cost of pembrolizumab, it is still unclear whether the use of first-line pembrolizumab for advanced NSCLC would still be cost-effective when the indication population was expanded from PD-L1 TPS greater than 50% to 1%. The current study investigated the economic outcomes of pembrolizumab as the first-line therapy in locally advanced or metastatic NSCLC patients without sensitive epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) alterations and with a PD-L1 TPS ≥ 1%. The cost-effectiveness analyses were made respectively in three PD-L1 TPS populations (≥50%, ≥20% and ≥1%), using the most recently reported survival data from KEYNOTE-042.

2. Materials and methods

2.1. Model structure

A mathematical model was established by combining a decision tree and the Markov approach to estimate the cost and effectiveness of using pembrolizumab versus chemotherapy as first-line treatments for locally advanced or metastatic NSCLC from the US payer's perspective. The Markov cycle length was 6 weeks and the structure were developed over a 20 years horizon. We adopted a 3% discount rate per year for both costs and outcomes [15]. Costs, life years (LYs), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) were estimated in each treatment strategy. The model structure and data were based on results of KEYNOTE-042 and supplemented with data from the United States publicly available databases and published literature. The model was developed using TreeAge Pro 2018 (TreeAge Software Inc., Williamstown, MA).

The model structure included 3 states to represent the progression of advance NSCLC: progression-free survival (PFS), progressive disease (PD), and death (Appendix Fig. 1). Patients were treated with pembrolizumab or chemotherapy in the PFS state until progression. Both pembrolizumab and chemotherapy groups could receive subsequent treatment until death when the disease progression or unacceptable toxic effects occurred. Adverse events that have great impact on the outcome were included which reported in KEYNOTE-042 trial.

2.2. Model survival and progression risk estimates

The estimates of OS for pembrolizumab group and chemotherapy group were based on the survival data from KEYNOTE-042. Firstly, we used the GetData Graph Digitizer (version 2.25; http://www.getdata-graph-digitizer.com/index.php) to extract the data points from the OS Kaplan-Meier curves published in the KEYNOTE-042, and these data points were then used to fit parametric survival models. The Weibull survival curves were matched to the number of patients in the three states over time because Weibull distributions are flexible and widely used in cancer survival analyses. Then, the shape parameter (γ) and the scale parameter (λ) were estimated from this fit and applied Kaplan-Meier curves by using R software package (http://www.r-project.org) with the method of Hoyle et al (Table 1) [16], and the mean OS time was denoted as S(t), we computed the cause-specific mortality M at cycle t as:

$$M = \frac{S(t) - S(t+1)}{S(t)}$$

while $S(t) = \exp(-\lambda t^{\gamma})(\lambda > 0; \gamma > 0)$

Finally, OS rates in each cycle were as follows:

1-exp (Scale*(_stage) ^Shape-Scale*(_stage + 1) ^Shape)

The PFS rate for the two groups estimated by the same methods. We used this measure to estimate the OS rate and PFS rate for pembrolizumab (PD-L1 TPS ≥ 50%; ≥20%; ≥1%) and chemotherapy, respectively.

2.3. Utility estimates

Utility was applied to measure patient's preference for living at a particular health state, where 0 stood for the worst health and 1 for the best. It reflected the impact of the disease-related health states. We used utilities of 0.653 and 0.473 which were based on previously published article for the patients in the first-line chemotherapy treatment and the subsequent treatment, respectively [17]. We calculated health utilities based on quality of life data (QLQ-C30 GHS/QOL) presented in the KEYNOTE-024 trial because the KEYNOTE-024 trial has the same treatment in experimental group and control group. In health-related quality-of-life results of KEYNOTE-024 trial [18], the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 items (QLQ-C30) questionnaire was applied to assess QOL. The result showed that pembrolizumab improved health-related QOL compared with chemotherapy. To calculate the improvement utility in pembrolizumab compared to chemotherapy, the utility of improvement was estimated by dividing the QLQ-C30 score by 126 (the maximum value of QLQ-C30 score). At baseline, the mean QLQ-C30 QOL score was 62.2 (utility of 0.494) in pembrolizumab group and 59.9 (utility of 0.475) in the chemotherapy group. After 15 weeks follow-up, the pembrolizumab group had a mean QLQ-C30 QOL score of 71.0 (utility of 0.563), and the chemotherapy had a mean QLQ-C30 QOL score of 63.7 (utility of 0.506). The incremental utility was 0.038. With the addition of the incremental utility to the utility of chemotherapy (0.653), and the utility of pembrolizumab was 0.691 (Table 1).

2.4. Cost inputs

Only direct medical costs were considered, including drug costs, costs of radiographic tests, cost of administration, cost of laboratory and adverse events (AEs) costs. The patients in pembrolizumab group were treated with 200 mg pembrolizumab intravenously once every 3 weeks, with the maximum cycle of 35. The chemotherapy group patients were treated with carboplatin plus paclitaxel 200 mg/m^2 or pemetrexed 500 mg/m^2. 49% and 51% patients in chemotherapy group were given paclitaxel plus carboplatin and pemetrexed plus carboplatin, respectively. After completing at least four cycles of platinum-doublet chemotherapy, 3% of patients treated with paclitaxel plus carboplatin and 29% of patients treated with pemetrexed plus carboplatin were receiving pemetrexed maintenance therapy (500 mg/m^2 every 3 weeks) in KEYNOTE-042 trial. For chemotherapy dosing, we used a standard area under the concentration curve of 6 mg/mL/min and assumed male sex, 65 years of age, weight of 70 kg, height of 70, body surface area 1.84m^2, and serum creatinine of 1 [19]. The price was derived from the Centers for Medicare & Medicaid Services and published articles [20–23], and the details were shown on Table 1. The costs of radiographic tests included a computed tomography (CT) (every 6 weeks treatment and every 9 weeks after progression) [22]. Adverse events (AEs) with a frequency of greater than 5% and higher than grade 3 were included. The costs related to AEs were calculated by multiplying the incidence of the serious AEs by the costs of managing the serious AEs per event. AEs costs were based on the data from previously published studies [24,25]. All information regarding the drug dose and costs were listed in Table 1. The subsequent therapy was based on KEYNOTE-042.

2.5. Sensitivity analysis

One-way sensitivity analyses were conducted to estimate the plausible changes of ICERs by varying each key input parameter, as shown in Table 1. The probabilistic sensitivity analysis was performed to estimate the probability of pembrolizumab treatment being cost-effective compared to chemotherapy treatment in all three PD-L1 TPS populations (≥1%, ≥20% and ≥50%) at a willing-to-pay (WTP) threshold of $150,000 [21]. 1000 Monte Carlo simulations were conducted by inputting values drawn from their statistical distributions which were showed in Table 1.

3. Results

3.1. Base case results

For the previously untreated locally advanced or metastatic NSCLC patients without sensitizing EGFR or ALK alterations, pembrolizumab compared to the platinum-based combination chemotherapy provided an additional 1.13 LYs, 0.82 LYs and 0.69 LYs in the PD-L1 TPS greater than 50%, 20% and 1% populations, respectively. Compared to chemotherapy treatment, the mean incremental costs and QALYs of the pembrolizumab treatment were $86,164.87 and 0.63, $74,562.25 and 0.46 and $70,886.65 and 0.39 for the populations with a PD-L1 TPS ≥ 50%, ≥20% and ≥1%, respectively. The ICERs per QALY for the pembrolizumab versus the chemotherapy were $136,228.82 in the TPS ≥ 50% population, $160,625.98 in the TPS ≥ 20% population and $179,530.17 in the TPS ≥ 1% population (Table 2).

3.2. Sensitivity analysis

The results of one-way sensitivity analysis were showed in Fig. 1. The variables found to have the greatest influence on the ICERs were similar in all three TPS populations (≥50%, ≥20% and ≥1%): the cost of pembrolizumab, the utility of PFS in pembrolizumab group and the utility of PFS in chemotherapy group. Pembrolizumab as first line treatment in NSCLC can be cost-effective compared with platinum-doublet chemotherapy if the cost of pembrolizumab would be reduced by 3% and 7% in patients with TPS greater than 20% and 1%, respectively, at a WTP threshold of $150,000 per QALY.

The results of probabilistic sensitivity analyses suggested that the probability of pembrolizumab being cost-effective compared with chemotherapy was 53.3%, 51.3% and 48.3% at a WTP threshold of $150,000 per QALY in the TPS ≥ 50%, ≥20% and ≥1% populations, respectively (Fig. 2 and Appendix Fig. 2). The results of the two-way sensitivity analyses showed that the value of ICERs were lower than $150,000 per QALY in the population with TPS ≥ 50%, but higher than $150,000 per QALY in the populations with TPS ≥ 20% and ≥1% across the majority of utility combinations (Appendix Fig. 3).

4. Discussion

Reports of the clinical benefit from pembrolizumab monotherapy in a clinical study caused great excitement among both oncologists and patients. However, the widespread use of these agents comes with a sharp increase in health resource consumption, which is of concern to administrators and patients, especially the indication has expanded to the advanced NSCLC patients with PD-L1 TPS of 1% or greater [26].

There are some cost-effectiveness studies that investigated pembrolizumab monotherapy as the first-line treatment in advanced NSCLC patients with a PD-L1 TPS ≥ 50% based on KEYNOTE-024 [24,27–29]. Three of these studies reported by Huang M, Georgieva and Christos C demonstrated that pembrolizumab was cost-effective compared with platinum-based chemotherapy in US and France [24,27,28]. However, it was not a cost-effective strategy in United Kingdom and China based on the studies conducted by Georgieva M and Liao W [27,29]. In our study based on KEYNOTE-042, pembrolizumab is cost-effective in patients with TPS ≥ 50% but not in patients with TPS ≥ 20% an ≥1% for US payers. Based on the KEYNOTE-042 trail and a WTP of $26,508/QALY in China, Kexun Zhou reported that pembrolizumab as the first-line treatment compared to chemotherapy is expected to obtain an ICER gained of $36,493/QALY, $42,311/QALY and $39,404 /QALY in the patients with TPS ≥ 50%, ≥20% and ≥1%, respectively, all of which were not indicated to be cost-effective [30].

To our knowledge, we performed the first study to examine the cost-effectiveness of pembrolizumab versus platinum-based chemotherapy in three PD-L1 TPS populations (≥50%, ≥20% and ≥1%) from the perspective of US payers. On the basis of our model, pembrolizumab cost $136,228.82, $160,625.98 and $179,530.17 per additional QALY gained compared with chemotherapy in the TPS greater than 50%, 20% and 1% populations, respectively. The probabilistic sensitivity analyses suggested a high likelihood that pembrolizumab would be considered cost-effective at a WTP threshold of $150,000 per QALY in the TPS ≥ 50% population but not in the populations with TPS ≥ 20% or TPS ≥ 1%, as recommended by Neumann et al [31]. The further one-way sensitivity analysis confirmed these results, showing that the cost of pembrolizumab was a critical influential factor for all the populations. In other words, it would be cost-effective with the value of ICER below $150,000 per QALY for all the population by reducing the cost of pembrolizumab.

However, the PFS and OS subgroup analyses on the populations with TPS ≥ 1% and TPS ≥ 20% did not exclude the TPS ≥ 50% population, where the majority of benefit occurs. Therefore, the results of cost-effectiveness analyses in the TPS ≥ 1% and TPS ≥ 20% populations are better than the actual situation in the 1–49% and 20–49% subsets, as the nearly 600 patients with TPS ≥ 50% improve the magnitude of pembrolizumab benefit and were not excluded. Despite all this, our results still showed pembrolizumab is estimated to not be cost-effective compared with platinum-based chemotherapy in the populations with TPS ≥ 1% and TPS ≥ 20% at a WTP threshold of $150,000 per QALY. In addition, the cost-effectiveness analysis was not performed in the TPS 1–49%, 1–19% and TPS 20–49% populations because

Table 2
Baseline results in pembrolizumab and chemotherapy groups in three PD-L1 TPS populations (≥50%, ≥20% and ≥1%).

Strategies and Scenarios	Total cost, $	LYs	QALYs	ICER per LY[a]	ICER per QALY[b]
TPS ≥ 50%					
Pembrolizumab	261 848.45	3.68	2.10	76 390.48	136 228.82
Chemotherapy	175 683.59	2.55	1.47	–	–
TPS ≥ 20%					
Pembrolizumab	249 065.60	3.36	1.93	90 965.81	160 625.98
Chemotherapy	174 503.35	2.54	1.47	–	–
TPS ≥ 1%					
Pembrolizumab	239 205.03	3.17	1.83	101 763.74	179 530.17
Chemotherapy	168 318.38	2.48	1.44	–	–

Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life-year; PD-L1, programmed death ligand 1; QALY, quality-adjusted life-year; TPS, tumor proportion score.

[a] Compared to chemotherapy ($/LY).

[b] Compared to chemotherapy ($/QALY).

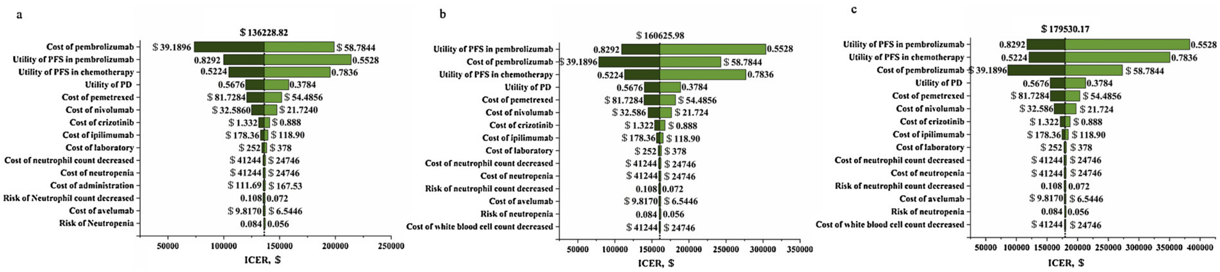

Fig. 1. Tornado diagram for one-way sensitivity analysis. a, Pembrolizumab vs chemotherapy in PD-L1 tumor proportion score (TPS) greater than 50% population. The parameters tested in this one-way sensitivity analysis were displayed in the right of the figure. The vertical dotted line represents ICER $136,228.82/QALY (the results of baseline analysis) b, Pembrolizumab vs chemotherapy in PD-L1 TPS greater than 20% population. The parameters tested in this one-way sensitivity analysis were displayed in the right of the figure. The vertical dotted line represents ICER $160,625.98/QALY (the results of baseline analysis) c, Pembrolizumab vs chemotherapy in PD-L1 TPS greater than 1% population. The parameters tested in this one-way sensitivity analysis were displayed in the right of the figure. The vertical dotted line represents ICER $179,530.17/QALY (the results of baseline analysis).

no PFS data was reported for these subgroups in the original trial. On the other hand, results of the detailed subgroup analyses demonstrated that the ICER of pembrolizumab could be improved with the use of clinical and pathological parameters to select patients (Appendix Table 1). Given the above-mentioned caveats, in the TPS ≥ 20% and ≥1% populations, pembrolizumab was cost-effective for patients with smoking history, locally advanced, squamous histologic type and ECOG 0.

In a cost-effectiveness analysis based on KEYNOTE-024 by Huang M, pembrolizumab yielded an expected gain of 1.05 QALYs and an incremental cost of $102,439 compared with chemotherapy in the TPS 50% or greater population, resulting an ICER of $97,621/QALY [24]. In our model, pembrolizumab yielded additional 0.63 QALYs and an incremental cost of $88,752 compared with chemotherapy in the TPS ≥ 50%, resulting an ICER of $136,228.82/QALY. It seemed that our value of ICER in the same population was higher than that report by Huang M. However, the value of median OS of populations with TPS ≥ 50% received pembrolizumab in KEYNOTE-042 was lower than those reported in KEYNOTE-024 [9,14]. It may have relationship with enrolled patients in different regions of the world and have different subsequent therapies in two studies. We confirmed this in further subgroup analysis in the PD-L1 TPS ≥ 50% population (Appendix Table 1a).

As the outcomes from KEYNOTE-042 presented, pembrolizumab as first-line treatment was proved able to reap clinical benefits in all three PD-L1 TPS populations (≥1%, ≥20% and ≥50%). Later, the US FDA approved pembrolizumab as first-line treatment for patients with advanced NSCLC, PD-L1 TPS ≥ 1%, while the EMA has not yet put forward any definitive recommendation. According to the analysis report by G. Mountzios et al, pembrolizumab may not be the optimal treatment strategy for patients with TPS of 1–49%, since the rapid progression on treatment may impair their health instead [32]. However, according to the outcomes of KEYNOTE-189 and KEYNOTE-407, for patients with PD-L1 expression of 1–49%, it may be a better choice to apply the combination of platinum-based chemotherapy with pembrolizumab [33,34].

It is of great challenges to approve new drugs by solely relying on survival benefits. Despite the survival benefits displayed in certain clinical trials, immune checkpoint inhibitors were, in most cases, not cost-effective [27,29,35–38]. Even for payers of same clinical trial, outcomes of the cost-effectiveness analysis in different regions might be distinct [24,27–2938]. That is why different economic elements in different regions should be taken into account before drug approval. At the same time, physicians and administrators shall be aware of the significance of employing predictive markers to appropriate patient selection, thus to arrive at cost-effective strategies aiming to sustain our health care systems [32].

There are limitations to our analysis, also. First of all, we acknowledge that the KEYNOTE-042 trial is the only randomized phase III trial that compared pembrolizumab with platinum-based chemotherapy in NSCLC patients with a PD-L1 TPS ≥ 1%. It is a large and well-designed trial, but our model is essentially reliant on the validity and generalizability of the trial and any biases within the trial will be reflected in our study. Second, our model is established with Weibull function to project long term PFS and OS beyond the observational time of the trial, and it is an inevitable limitation in our analysis. Third, because of the absence of head-to-head trials in the population with PD-L1 TPS ≥ 1%, this study did not include other competing strategy, such as combination pembrolizumab and chemotherapy. The current research needs to be updated by incorporating these novel competing alternatives. Fourth, due to the model hypothesis, the exploratory nature of the subgroup analyses, and the small sample size in each subgroup, the results of subgroup analyses in the current study should be interpreted with caution. Fifth, the costs of grade 1/2 AEs were

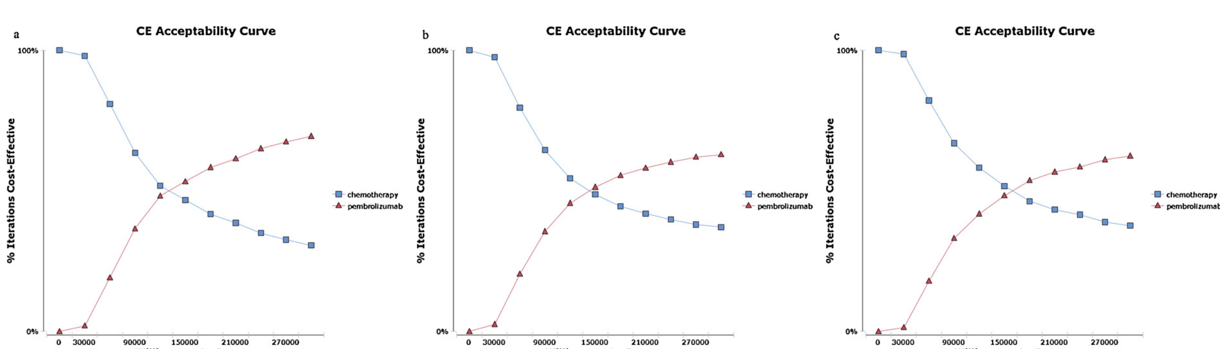

Fig. 2. Acceptability curves for the choice of pembrolizumab and chemotherapy treatment strategies at different willingness-to-pay (WTP) thresholds in patients with metastatic NSCLC. a, Pembrolizumab vs chemotherapy in PD-L1 tumor proportion score (TPS) greater than 50% population. b, Pembrolizumab vs chemotherapy in PD-L1 TPS greater than 20% population. c, Pembrolizumab vs chemotherapy in PD-L1 TPS greater than 1% population.

excluded and the effects of immune-related AEs (irAEs) were not considered separately because there was no evidence demonstrating it has significant difference in managing irAEs and non-irAEs, which might underestimate or overestimate the benefits of pembrolizumab. Sixth, the immunotherapy-related AEs, such as pneumonitisa, myocarditis and encephalitis are rare but the cost of treatment is very high. Therefore, including all AEs with an incidence greater than 1% will more accurately evaluate the AEs cost in patients with pembrolizumab. In this study, only grade 3–4 AEs with an incidence > 5% were included, the benefit of pembrolizumab may be overestimated.

In conclusion, from the perspective of US payers, first-line treatment with pembrolizumab is a cost-effective strategy when compared to platinum-based chemotherapy in locally advanced or metastatic NSCLC patients with PD-L1 TPS ≥ 50% and without EGFR and ALK mutations, but not in the TPS ≥ 20% and TPS ≥ 1% populations.

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Declaration of Competing Interest

All of the authors have indicated that they have no conflicts of interest with regard to the content of article. This manuscript is original and has not been previously published, nor has it been simultaneously submitted to any other journal.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.10.017.

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