



# Cost-effectiveness analysis of pembrolizumab monotherapy and chemotherapy in the non-small-cell lung cancer with different PD-L1 tumor proportion scores



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## ABSTRACT

**Objectives:** This study aimed to assess the cost-effectiveness of pembrolizumab monotherapy compared with chemotherapy as first-line treatment in patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with different tumor proportion scores (TPS), from perspectives of payers in China.

**Materials and methods:** Basic information was derived from the KEYNOTE-042 trial. A Markov model was developed to simulate the process of NSCLC. Model inputs were based on published clinical trials and previous literatures. Costs were calculated from perspectives of payers in China. Sensitivity analyses were conducted to explore the impact of uncertainty.

**Results:** Treatment with pembrolizumab monotherapy for patients with high TPS ( $\geq 50\%$ ) was estimated to increase costs by \$65,322 compared with chemotherapy, with a gain of 1.79 quality adjusted life years (QALYs) for an incremental cost-effectiveness ratio (ICER) of \$36,493 per QALY. For patient population with TPS  $\geq 20\%$ , the ICER was \$42,311 per QALY, while the corresponding ICER was \$39,404 per QALY for patients with TPS  $\geq 1\%$ . Sensitive analyses for three different TPS populations were similar, which indicated the cost of PFS state in pembrolizumab arm and the price of pembrolizumab were the most influential factors in our study.

**Conclusion:** ICERs yield by pembrolizumab monotherapy among different TPS populations were beyond the threshold we set, three times of the Gross Domestic Product per Capita of China in 2018 (\$26,508/QALY). It is not a cost effective choice compared with standard chemotherapy for patients with locally advanced or metastatic NSCLC from the perspective of Chinese payer, regardless of TPS. Deeper discount of its current price would make pembrolizumab a preferable choice.

## 1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide and can be broadly classified into two types: non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). The former represents 85% of all lung cancer [1].

In the KEYNOTE-024 trial, pembrolizumab was associated with significantly better health outcomes in patients with advanced NSCLC and programmed death ligand 1 (PD-L1) expression on at least 50% of tumor cells, compared to platinum-based chemotherapy [2]. Based on this, The National Comprehensive Cancer Network (NCCN) Panel recommends single-agent pembrolizumab as first-line therapy for patients with advanced nonsquamous or squamous NSCLC; with PD-L1

expression levels of 50% or more, and with negative or unknown tests results for EGFR mutations, BRAF V600E mutations, ALK rearrangements, and ROS1 rearrangements. Meanwhile, for patients without (or unknown) genetic alterations whose PD-L1 levels are less than 50% or unknown, pembrolizumab plus standard chemotherapy of pemetrexed and a platinum-based drug was recommended by the NCCN Panel, based on the KEYNOTE-189 trial [3].

Recently, the KEYNOTE-042 trial published its high-profile findings [4]. The results indicated that effect of immunotherapy was greatest in patients with a TPS of 50% or greater, but remained significant in patients with a TPS of 1% or greater. This finding suggested pembrolizumab monotherapy could be a reasonable first-line treatment option for patients with lower PD-L1 expression levels.

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Previous study conducted from the perspective of payers in the United States suggested pembrolizumab was projected to be cost effective as first-line treatment in metastatic NSCLC expressing high levels of PD-L1, when compared to platinum-based chemotherapy [5]. Since the KEYNOTE-042 trial confirmed that pembrolizumab could be extended to NSCLC patients with a TPS as low as 1% and subjects from East Asia accounted for the largest proportion, we conducted economic analysis to evaluate the cost-effectiveness of pembrolizumab monotherapy as first-line treatment in patients with different TPS from the Chinese payer perspective.

## 2. Materials and methods

### 2.1. Patients

Medical information was derived from the KEYNOTE-042 trial. Patients enrolled were randomly assigned to receive pembrolizumab 200 mg every 3 weeks or platinum-based chemotherapy. For chemotherapy arm, carboplatin, paclitaxel and pemetrexed were administered according to body surface area or area under the curve. Treatment-related adverse events of grade 3 or worse severity was pneumonitis in patients who received immunotherapy, while myelosuppression occurred more commonly in the chemotherapy arm.

### 2.2. Model structure

A Markov model was designed to simulate the process of locally advanced or metastatic NSCLC. Plot Digitizer software was used to extract the survival probabilities from the published survival curves in the KEYNOTE-042 trial. And Microsoft Excel was used to calculate transition probabilities, in order to fit curves from the KEYNOTE-042 trial. Kaplan-Meier curves for the calibrated model are shown in Figures (Fig. 1).

### 2.3. Utilities

As the KEYNOTE-042 trial did not collect the information of quality of life, utilities of each health states in both pembrolizumab monotherapy and chemotherapy arms were obtained from previously published study (0.761 for PFS, 0.687 for PD and 0 for death) [6].

### 2.4. Measurement of costs

We conducted this study from a third-party payer's perspective, only direct medical cost was calculated, which included the cost of drugs, test, treatment for grade  $\geq 3$  AEs and hospital administration. The dosage of chemotherapy agents based on body surface area, average weight and height of Asian population was cited [7]. Notably, subsequent treatment was not well specified in the original article. According to the National Comprehensive Cancer Network Clinical Practice Guidelines, patients with metastatic NSCLC who have progressed after first-line therapy with pembrolizumab, platinum-based doublet therapy is recommended. And for NSCLC patients without a sensitizing EGFR mutation or ALK translocation, nivolumab was recommended as second-line treatment (category 1A). Thus, we assumed patients in the pembrolizumab arm received platinum-based doublet therapy ((carboplatin plus paclitaxel or pemetrexed)) as subsequent treatment, while subjects in its competitor arm received nivolumab after progression. Cost of drugs was adjusted based on treatment duration in the KEYNOTE-042 trial. All the costs were derived from West China Hospital, Sichuan University and converted to US dollars according to the exchange rate of \$1 = RMB 6.7105 on 22 April 2019.

### 2.5. Cost-effectiveness analysis

The time horizon was ten years. Half cycle correction was applied in

the model. Quality adjusted life years (QALY) gained and an estimate of overall costs were used to evaluate the incremental cost-effectiveness ratio (ICER). Cost and QALY were discounted at 3% annually.

### 2.6. Sensitivity analysis

One-way sensitivity analysis was performed to explore the potential influences of different parameters, the results of which were shown as a tornado diagram to identify key factors. Monte Carlo simulation of 1000 individuals was performed to figure out uncertainty strategies. According to the guidelines of World Health Organization for cost-effective analysis, the threshold of willingness to pay (WTP) was evaluated at \$26,508/QALY, three times of the Gross Domestic Product per Capita (GDP) of China in 2018 [8].

## 3. Results

### 3.1. Basic outcomes

The results generated by the Markov models revealed as the TPS increased, pembrolizumab provided better efficacy but higher cost for patients with locally advanced or metastatic NSCLC. For patients with TPS  $\geq 50\%$ , health outcomes was more than twice with management of pembrolizumab as compared to chemotherapy (2.81 VS 1.02 QALYs) and the associated ICER was \$36,493/QALYs. In the remaining two arms, the use of pembrolizumab provided additional 1.21 QALYs in TPS  $\geq 20\%$  population and 1.12 QALYs in TPS  $\geq 1\%$  population when compared to its competitor, leading to an ICER of \$42,311/QALYs and \$39,404/QALYs, respectively (Table 1). ICERs yield by pembrolizumab in all three arms were beyond the threshold we set.

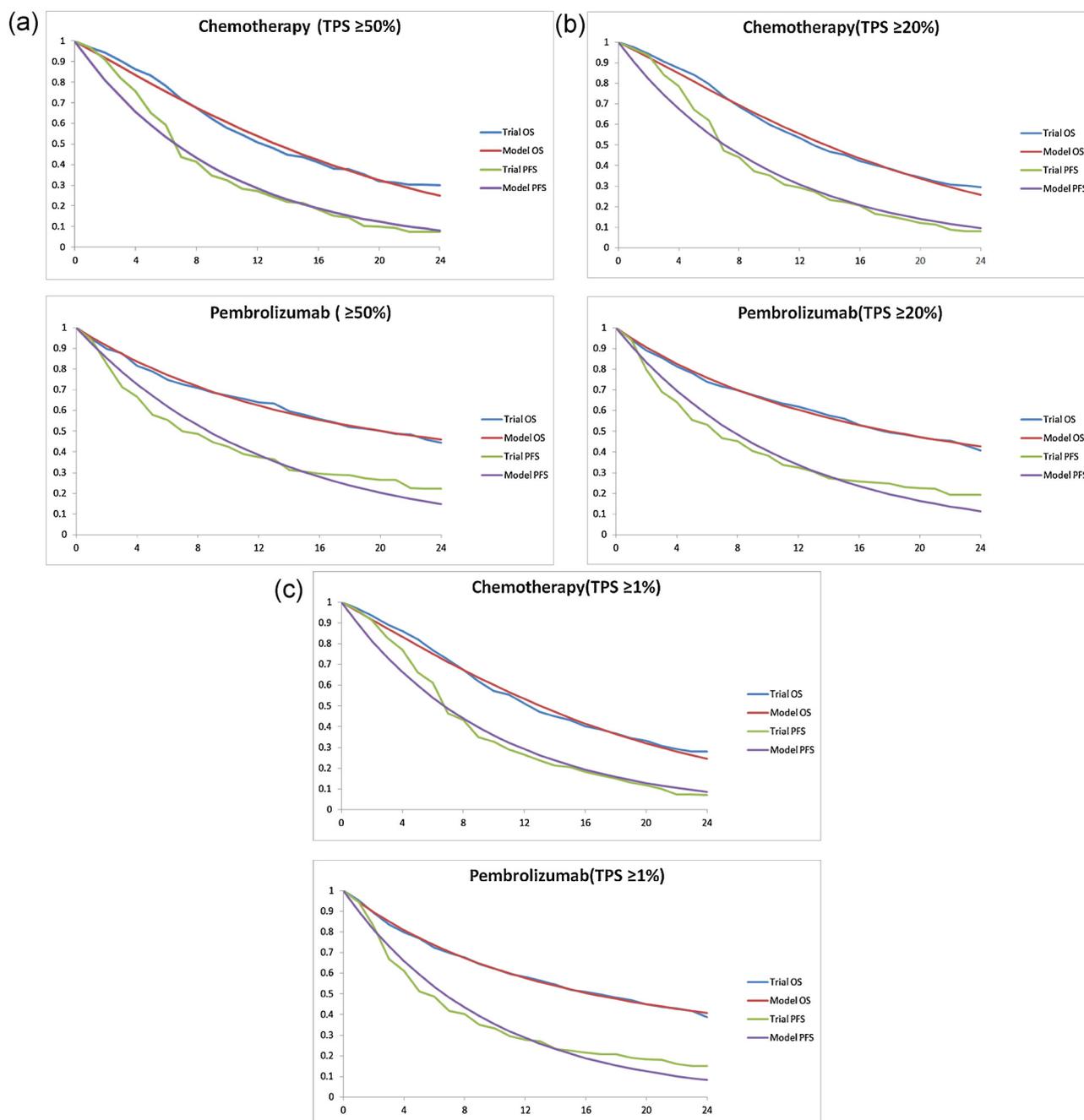
### 3.2. Sensitivity analysis

Variables were varied with a range of  $\pm 30\%$  in one-way sensitive analyses. Although there was slight difference in three populations, cost of PFS state in pembrolizumab arm, the price of pembrolizumab and utility of progressed were the most influential factors in our study. The cost-effectiveness analysis was also sensitive to the cost of PD state in two arms, as well as the cost of PFS state and the price of chemotherapy. Expenditure on the test, management of AEs and hospitalization had minor influence on the ICER. We also performed one-way sensitivity analyses to determine the price, at which pembrolizumab would be cost effective when compared to the chemotherapy. The results suggested that pembrolizumab would be an optimal choice at \$1,943, \$1799 and \$1935 (100 mg/4 ml) for patients with TPS  $\geq 50\%$ ,  $\geq 20\%$  and  $\geq 1\%$ .

## 4. Discussion

The inspiring results of the KEYNOTE-042 trial indicated pembrolizumab monotherapy could be extended to NSCLC patients without EGFR or ALK alterations and with low TPS in the first-line treatment [4]. We were deeply interested in the associated economic value of pembrolizumab monotherapy among NSCLC patients with different TPS. According to our analysis, although pembrolizumab yield the lowest ICERs among patient population with high TPS ( $\geq 50\%$ ), it was still beyond the threshold we set. As a result, we did not consider pembrolizumab monotherapy is a cost-effective choice compared with standard chemotherapy for patients with locally advanced or metastatic NSCLC, regardless of TPS. Deeper discount of its current price in China would make pembrolizumab a preferred choice.

As soon as the result of KEYNOTE-024 was published, cost effectiveness analyses of pembrolizumab and chemotherapy were evaluated. Min Huang and co-workers conducted the study from a US third-party public healthcare payer perspective [5]. Positive conclusion was drawn that pembrolizumab is projected to be an optimal option compared



**Fig. 1.** Calibrated models. (a): For patients with  $TPS \geq 50\%$ . (b): For patients with  $TPS \geq 20\%$ . (c): For patients with  $TPS \geq 1\%$  OS, overall survival; PFS, progression-free survival; TPS, tumor proportion score.

with standard-of-care platinum-based chemotherapy as first-line treatment for metastatic NSCLC expressing high levels of PD-L1 ( $TPS \geq 50\%$ ). On the contrary, Liao et al suggested pembrolizumab is not likely to be cost effective for Chinese patients [9]. Notably, the ICER for patients with PD-L1 expression on at least 50% was much higher than ours (\$103,128/QALY VS \$36,493/QALYs), regardless the fact that clinical efficacy observed in high TPS population is significantly better in KEYNOTE-024 than that reported in KEYNOTE-042. This may be associated with the impact of utility. They used 0.65 for the non-progression state and 0.47 for the progression state, while we cited the updated health outcomes (0.761 for PFS and 0.687 for PD). Their sensitivity analysis indicated the increase of utility of non-progression resulted in the decrease of ICER, which was consistent with our findings among high TPS population. We consider this could be a potential factor contributing to the difference between two studies.

With regard to pembrolizumab in combination of chemotherapy in the first-line treatment of NSCLC, Ralph P et al did relative cost-effectiveness analysis based on KEYNOTE-189 in overall trial population, as well as by PD-L1 subgroup [10]. Although ICERs generated by the combination therapy varies within subgroups, it is either near or well below the WTP threshold compared to chemotherapy. Thus, authors suggested pembrolizumab plus chemotherapy could be a cost effective first-line treatment for eligible metastatic NSCLC patients. As there is no general agreement on an ICER threshold for the USA, the two studies mentioned above adopted a range of WTP threshold from \$100,000 to \$180,000 per QALY, which was much higher than that in our study. Lower threshold could be a contributory factor to our negative results.

Interestingly, Ralph P et al found the estimated ICER is lower in patients with PD-L1 1–49% as compared to PD-L1  $\geq 50\%$  in the subgroup analysis, which was similar with ours. According to our results,

**Table 1**  
Cost-effectiveness analysis.

Variables	Chemotherapy			Pembrolizumab		
	TPS $\geq$ 50%	TPS $\geq$ 20%	TPS $\geq$ 1%	TPS $\geq$ 50%	TPS $\geq$ 20%	TPS $\geq$ 1%
<b>Cost (\$)</b>						
PFS state	9,160	9,812	9,358	71,326	63,215	55,359
PD state	20,686	20,859	20,124	23,842	18,652	18,256
Total costs	29,846	30,671	29,482	95,168	81,867	73,615
Incremental costs				65,322	51,196	44,133
<b>Effectiveness (QALYs)</b>						
PFS state	0.60	0.64	0.62	0.79	0.70	0.62
PD state	0.42	0.43	0.42	2.02	1.58	1.54
Total effectiveness	1.02	1.07	1.04	2.81	2.28	2.16
Incremental effectiveness				1.79	1.21	1.12
<b>ICER (\$/QALY)</b>				36,493	42,311	39,404

PFS, progression-free state; PD, progressive disease.

QALYs, quality adjusted-life years; ICER, incremental cost-effectiveness ratio.

treatment with pembrolizumab led to the highest ICER of \$42,311 per QALY in patients with TPS  $\geq$  20%, rather than in patients with TPS  $\geq$  1%. One reason could be highlighted. Chemotherapy was associated the best efficacy in patients population with middle TPS, which resulted substantively higher drug acquisition costs than that in the low TPS population. This should be verified in other populations or malignancies, in order to make better understanding whether these findings are replicable or part by chance. And this may provide doctors with clinical value in guiding the choice of therapies for patients with different TPS.

One-way sensitivity analyses indicated cost of PFS state in pembrolizumab arm, the price of pembrolizumab and utility of progressed were the most influential factors in our study. Further analysis indicated the price of pembrolizumab's discounts varied among different TPS populations. But we have to admit, compared with other countries or regions, China enjoys the lowest price of pembrolizumab. Even in this case, it does not make pembrolizumab an optimal choice for patient population with different TPS.

This study is not without limitations. First and most important, basic information was retrospectively collected from a phase 3 trial, which was not patient-level data in clinical practice. The dosage of chemotherapy drugs is usually based on body surface area and it should be adjusted according to the physical conditions of patients. This may varied among individuals. Besides, three TPS populations may have different duration of treatment and subsequent therapy is not limited to docetaxel or nivolumab. Platinum-based chemotherapy (eg, cisplatin plus gemcitabine, carboplatin plus paclitaxel) can be an alternative choice for patients who did not receive platinum previously. And a part of patients may not receive second-line or later treatment in the real-world clinical practice. Second, base-case cost was derived from West China Hospital, Sichuan University. Despite of the fact that it can represent drug price in most Chinese medical centers, there remains little difference between different hospitals or regions. This may affect the generalizability of our research.

In conclusion, although pembrolizumab monotherapy significantly prolonged overall survival among NSCLC patients with different TPS, the results of our study suggested it was not an optimal strategy from a Chinese cost-effectiveness perspective. Deeper discount of its price is still needed.

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## Declaration of Competing Interest

None.

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