Research Article

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Cost–effectiveness analysis of pembrolizumab for patients with advanced esophageal cancer at PD-L1 combined positive score ≥10

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Aim: Due to the high price of pembrolizumab, it is still unknown whether the use of pembrolizumab for advanced esophageal cancer would be a cost-effective option for patients whose PD-L1 combined positive score is ≥10. **Methods:** A Markov simulation model was performed based on clinical trial KEYNOTE-181. Incremental cost–effectiveness ratios were calculated to compare the two treatments. **Results:** The total costs were US$193,575.60 and $8789.24 for pembrolizumab and chemotherapy treatment, respectively. The pembrolizumab group produced 0.93 quality-adjusted life years (QALYs), while the chemotherapy group produced 0.58 QALYs. Thus, patients in the pembrolizumab group spent an additional US$184,786.36 and produced 0.35 QALYs more than the chemotherapy group, which resulted in an incremental cost–effectiveness ratio of US$527,961.03 per QALY. **Conclusion:** For patients with advanced esophageal cancer whose PD-L1 combined positive score is ≥10, pembrolizumab is not a cost-effective second-line therapy versus chemotherapy from the US payer perspective.

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Cancer-related death has become a great health issue in many countries and is mainly caused by rapid population growth and aging. There were 473,000 new cases of esophageal cancer (EC) and 436,000 EC-related deaths in 2017 and approximately 18,000 new cases were diagnosed in 2019 [1]. The sixth most common cause of cancer-related death worldwide is EC. Additionally, metastatic EC is a fatal disease, of which the prognosis is typically poor, with a median overall survival (OS) of less than a year. The areas with the highest prevalence of EC were Asia and Africa [2–4]. Fluoropyrimidine combined with platinum is recommended in current guidelines for first-line chemotherapy [5–7]. However, there are limited options for patients with metastatic EC after progression during first-line chemotherapy.

Anti-PD-1/PD-L1 treatments have shown significant tumor responses in patients with advanced EC [8,9]. Recently, several immune inhibitory pathway blockers, including pembrolizumab and nivolumab, targeting PD-1, as well as atezolizumab, durvalumab and avelumab, which inhibit PD-L1, have already been demonstrated to be effective and some of them have even been approved for clinical practice [10–13]. Pembrolizumab is a humanized, monoclonal anti-PD-1 antibody that has been proven to gain an obvious OS benefit with acceptable safety in patients with metastatic EC when the disease progresses during first-line therapies [14]. Recent studies have shown that pembrolizumab provides durable tumor responses in multiple tumor types [15]. The randomized phase III, open-label KEYNOTE-181 clinical trial demonstrated that pembrolizumab significantly prolonged OS and progression-free survival (PFS) versus chemotherapy for advanced EC in patients with PD-L1 combined positive score (CPS) ≥10 as second-line therapy [16].

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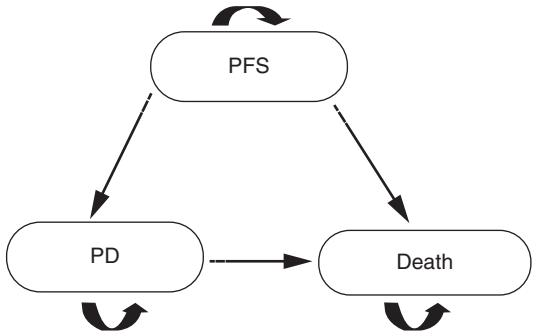

Figure 1. A Markov structure was built to compare the two treatments.
PD: Progressive disease; PFS: Progression-free survival.

Because pembrolizumab is expensive, it is still unknown whether the use of pembrolizumab for advanced EC would be a cost-effective option with patients whose PD-L1 CPS is ≥10. We therefore carried out this analysis to determine whether pembrolizumab was a cost-effective option from the US payer perspective.

Methods

Patients

We extracted the clinical data from the KEYNOTE-181 study. In total, 628 patients who were ≥18 years of age with histologically confirmed metastatic or locally advanced unresectable squamous cell carcinoma or adenocarcinoma of the esophagus from 154 sites in 32 countries were enrolled. A total of 314 versus 296 patients were randomly assigned to the pembrolizumab arm (PE) and chemotherapy arm (CH), respectively. There were no statistically significant differences between the two arms at baseline. The expression of PD-L1 at a CPS ≥10 was also well balanced between the two arms.

Treatment

The 314 patients in the PE group received 200 mg pembrolizumab every 3 weeks and the 296 patients in the CH group received standard chemotherapy including paclitaxel (80–100 mg/m^2) on days 1, 8 and 15 of each cycle (4 weeks), docetaxel (75 mg/m^2) on day 1 of each cycle (3 weeks) or irinotecan (180 mg/m^2) on day 1 of each cycle (2 weeks). Patients whose PD-L1 expression was at CPS of 10 or greater were included in our analysis. Radiological examinations were performed at week 9 and every 9 weeks thereafter to assess progressive disease. The mean (standard deviation) therapeutic time was 4.0 (5.0) months versus 3.1 (2.9) months in the PE group and CH group, respectively. Treatment-related adverse events (AEs) were evaluated throughout the entire study and were graded according to the National Cancer Institute Common Terminology Criteria (version 4.0) [16].

Economic model

The decision analysis Markov model was established to assess the cost–effectiveness of pembrolizumab versus chemotherapy as second-line therapy for advanced EC from the US payer perspective. The Markov model was implemented using TreeAge Pro 2019 software (TreeAge, MA, USA) and statistical analyses were performed using R software (version 3.6.3, www.r-project.org). PFS, progressive disease (PD) and death were described as three mutually incompatible health states in the model. At the beginning, advanced EC patients with a CPS of 10 or more entered the PFS state. Patients in the PFS state can progress to the PD state or directly to death. Patients in the PD state could progress to death or stay in the same state and death was described as an absorbing state (Figure 1). The model cycle length was 1 month and the model simulation runs lasted for 10 years. Quality-adjusted life years (QALYs), incremental cost–effectiveness ratio (ICER) and total cost were the outputs of this model. ICER equals the difference in costs between the two strategic therapies divided by the difference in effects. The PE group will become cost-effective only if the ICER of the two groups was below the willingness-to-pay (WTP) threshold of US$150,000 in the US.

We used GetData Graph Digitizer software to extract the survival curve from published OS curves from the published KEYNOTE-181 trial. Pseudoindividual patient data were generated using the algorithm derived by Hoyle and Henley, which can improve the estimation accuracy of survival time [17]. Next, 8A log-normal distribution was fitted to the OS curve in the PE group, as it provided the best fit among the exponential, log-logistic and log-normal distributions according to the Akaike information criterion, while a Weibull distribution was fitted to the CH group. We estimated the PFS curve using the same approach and log-normal distributions were fitted to

Table 1. Clinical efficacy, baseline input costs and baseline transition probability based on the KEYNOTE-181 trial.

Parameters	Pembrolizumab group	Chemotherapy group	Ref.
Costs per month $†			
Pembrolizumab	22,631.60 (18,105.28–27,157.92)	–	
Paclitaxel	–	170.60 (136.48–204.72)	
Docetaxel	–	287.30 (229.84–344.76)	
Irinotecan	–	129.40 (103.52–155.28)	
Tests	546 (436.80–655.20)	546 (436.80–655.20)	[20]
Major AEs	27.94 (22.35–33.53)	316.75 (253.40–380.10)	
Cost of PFS	23,205.54 (18,564.43–27,846.65)	1058.55 (846.84–1270.26)	
Cost of PD	558 (446.40–669.60)	558 (446.40–669.60)	[31]
Utility			
PFS	0.74		[23,24]
PD	0.58		[23,24]
Discount rate, %	3		[22]

†Basis of variables, ±20% of the base-case values.
AE: Adverse event; PD: Progressive disease; PFS: Progression-free survival.

both groups (Figure 2). The calculation of the time-dependent transition probability is treated in more detail in the supplement.

Costs & utility

Only direct costs were analysed in this study, including costs for drugs, tests (radiographic and laboratory), treatments for AEs and third-line therapy (Table 1). The prices of all the drugs were obtained on Drugs.com, 2020 [18]. In consideration of patients' geographic region in the KEYNOTE-181 study, a mean body-surface area of 1.75m^2 was adopted according to published literature [19–21]. The major AEs reported in the KEYNOTE-181 study were included in our analysis. A mean cost of three different chemotherapy regimens in the CH group was adopted because the exact number of patients in each regimen was not mentioned in the KEYNOTE-181 study. All costs were measured in US dollars and a discount rate of 3% per year was adopted for both costs and outcomes [22]. Utility was applied to reflect the impact of the disease-related health states, ranging from 0 for death to 1 for the best state. Because quality-of-life data could not be obtained from the KEYNOTE-181 trial, we used utilities of 0.74 and 0.58 for the PFS and PD states, respectively, according to previously published literature [23,24].

Sensitivity analysis

One-way probabilistic sensitivity analysis was conducted to evaluate the impact of related factors in the model. To explore their impacts on ICER, input parameters were varied within a range of ±20%. Additionally, a Monte Carlo simulation with 1000 simulations with 10,000 individuals was used to assess the probabilistic sensitivity of the model. US$150,000 per QALY was set as the WTP threshold in the USA [25] (Table 1).

Results

Baseline analysis

The total costs were US$193,575.60 and $8,789.24 for pembrolizumab and chemotherapy treatment, respectively. The PE group produced 0.93 QALYs, while the CH group produced 0.58 QALYs. Thus, patients in the PE group spent an additional US$184,786.36 and produced 0.35 QALYs more than the CH group, which resulted in an ICER of US$527,961.03 per QALY (Table 2).

Sensitivity analyses

The one-way sensitivity analysis is displayed in Figure 3. The cost of pembrolizumab was the most sensitive parameter influencing the results, as well as the utility of PD and PFS. When the cost of pembrolizumab ranged from US$18,105.28 to $27,157.92, the ICER ranged from US$432,471.09 to $645,786.60 per QALY, which were

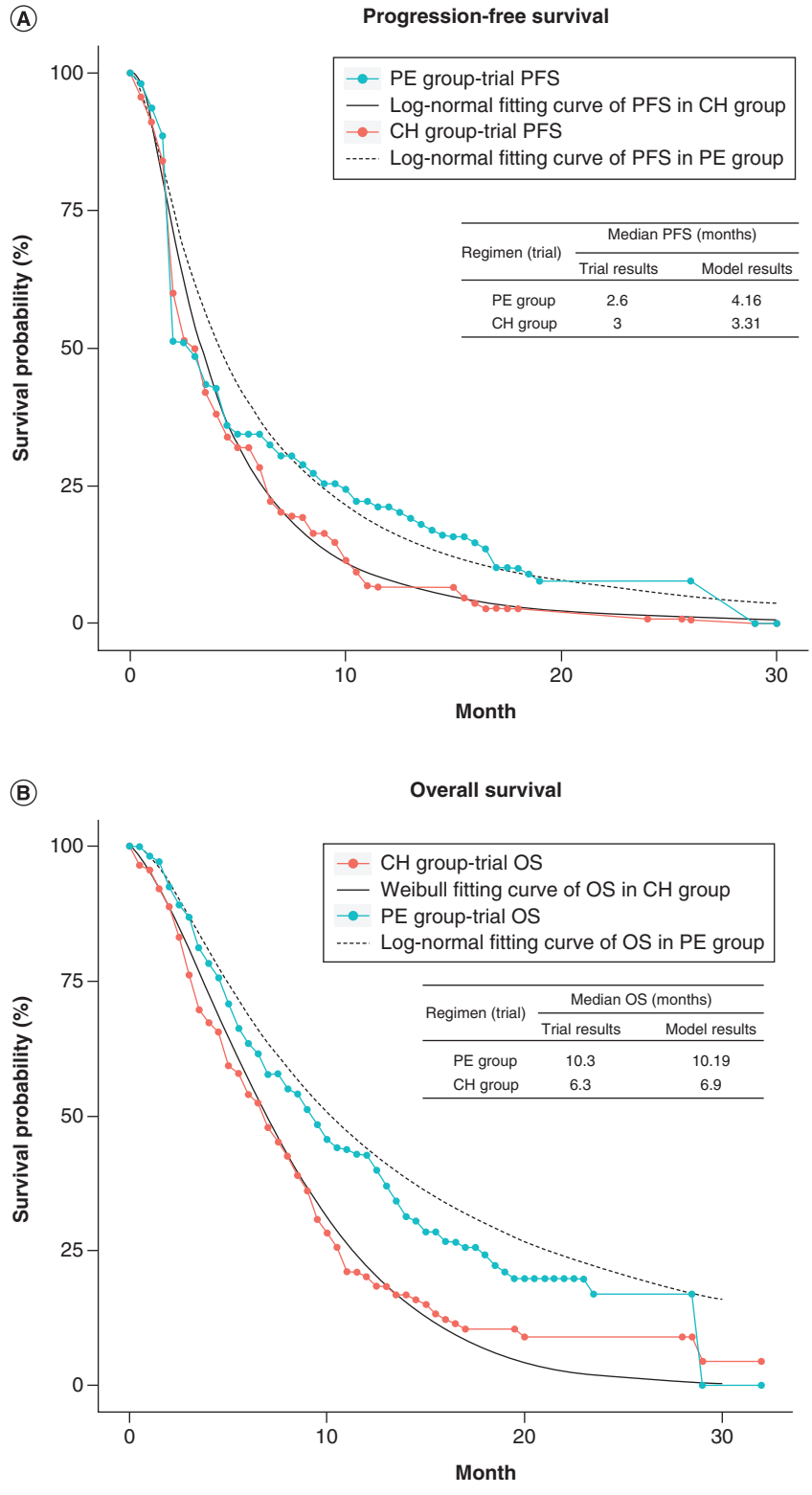

Figure 2. The original Kaplan–Meier. (A) PFS and **(B)** OS curves from the KEY-NOTE181 trial. Weibull and log-normal distributions were fitted to the two groups.
CH: Chemotherapy; OS: Overall survival; PE: Pembrolizumab; PFS: Progression-free survival.

Table 2. Results of base-case analysis of the pembrolizumab and chemotherapy groups.

Result	Pembrolizumab group	Chemotherapy group
Cost (US$)	193,575.60	8789.24
Incremental costs	184,786.36	
Effectiveness (QALYs)	0.93	0.58
Incremental effectiveness	0.35	
ICER (US$/QALYs)	527,961.03	

ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year.

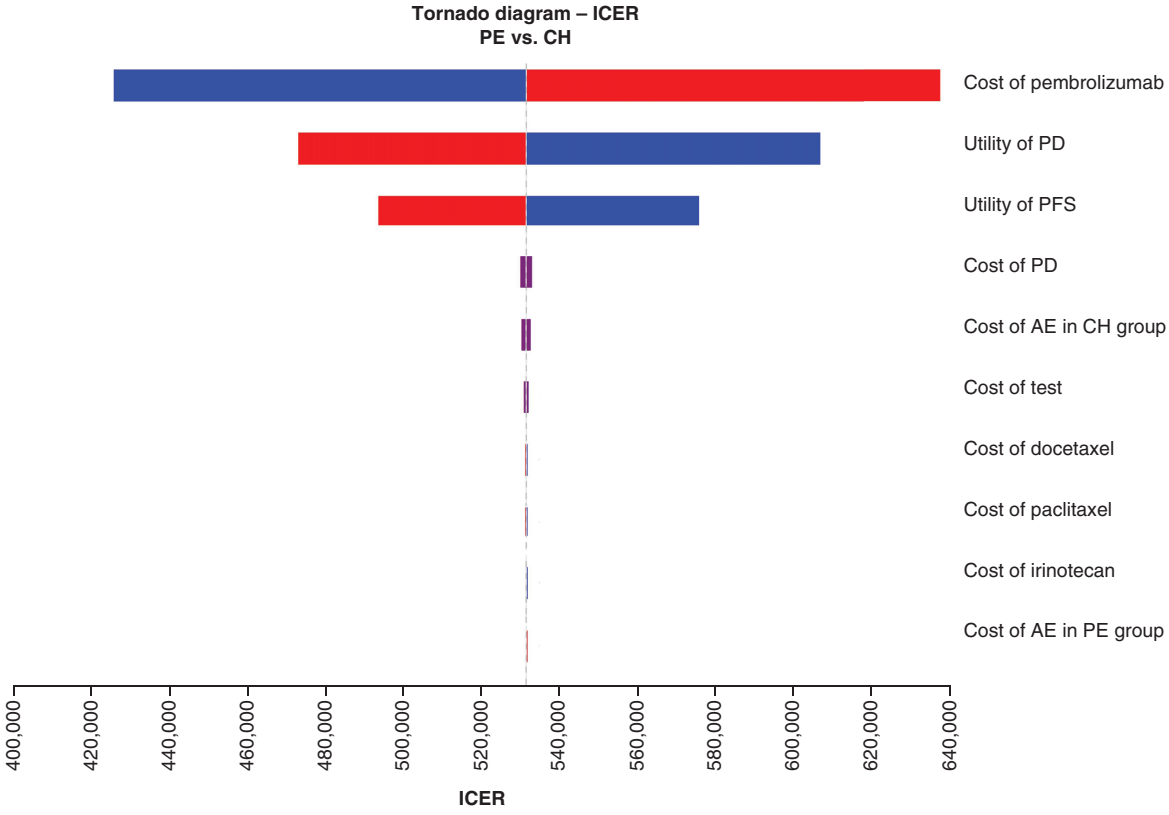

Figure 3. A one-way sensitivity analysis is shown in a tornado diagram. The impact of each parameter on the ICER is listed.
AE: Adverse event; CH: Chemotherapy group; ICER: Incremental cost–effectiveness ratio; PD: Progressive disease; PE: Pembrolizumab group; PFS: Progression-free survival.

all well above the WTP threshold of US$150,000 in the USA. Changing other parameters may somehow result in different costs and effectiveness but have little impact on the ICER. The acceptable curve shows that compared with standard chemotherapy, pembrolizumab was not a cost-effective option for patients with advanced EC with PD-L1 CPS ≥10 as second-line therapy at a WTP threshold of US$150,000 from the US payer perspective (Figure 4).

Discussion

EC remains a major cause of cancer-related mortality and economic burden worldwide. Patients who progress after first-line chemotherapy still have a shortage of second-line treatment and poor prognosis. Several kinds of immune checkpoint inhibitors (ICIs) of PD-1 have shown significant effects on different types of cancers. Pembrolizumab is a highly selective humanized monoclonal antibody that can not only induce dual ligand blockade of the PD-1 protein but also inhibit the immune response [26]. The KEYNOTE-181 study reported that pembrolizumab provided a clinically meaningful PFS and OS benefit as second-line therapy compared with standard chemotherapy in patients with advanced EC whose PD-L1 CPS ≥10 [16].

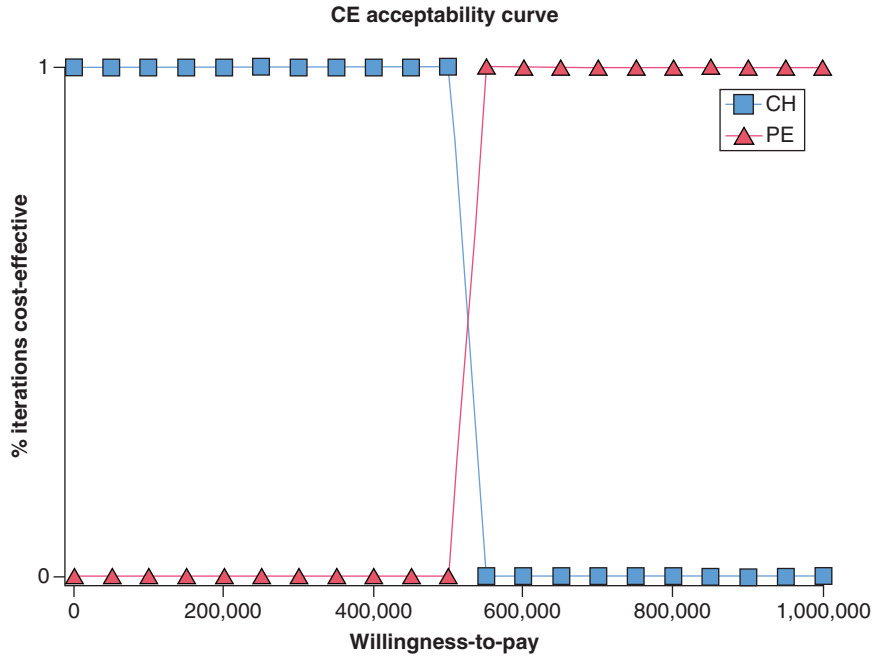

Figure 4. The acceptability curve of cost–effectiveness showed the probability at the current willingness-to-pay threshold.
CE: Cost-effective; CH: Chemotherapy group; PE: Pembrolizumab group.

According to our analysis, the ICER of the pembrolizumab group was US$527,961.03 per QALY, which was well above the current WTP of US$150,000 in the USA. Pembrolizumab will become a cost–effective option at a great reduction in pembrolizumab price. An analysis in France showed that pembrolizumab was cost–effective versus chemotherapy in the first-line therapy of patients with metastatic head and neck squamous cell carcinoma with PD-L1 expression at CPS ≥1 [27]. Similar analyses in the USA and Hong Kong showed that pembrolizumab is a cost–effective treatment when compared with platinum doublet chemotherapy as first-line treatment in non-small-cell lung cancer patients whose PD-L1 tumor proportion score was ≥50% [20,28]. A recent cost–effectiveness study showed that pembrolizumab will become cost-effective relative to chemotherapy at a price reduction of 93% or greater in patients with carcinoma *in situ* of the bladder, which is similar to our study [29].

Substantial progress has been made in recent years regarding ICI therapies, which provides new insights for advanced EC therapy. However, ICIs are often expensive, resulting in a significant economic burden on both patients and the health system. Therefore, our research was valuable to assess the cost-effective strategy with second-line treatment for advanced EC from a payer perspective. Despite the high cost of pembrolizumab, patients in the PE group experienced obviously lower treatment-related AEs than those in the CH group. Additionally, for patients with PD-L1 expression at CPS ≥10, the median duration of tumor response was longer in the PE group, which indicated a higher antitumor activity with pembrolizumab versus chemotherapy [16].

Nevertheless, our study has some limitations. First, our study was performed based on a published phase III trial instead of patients in the real world. Apparently, our model could not totally replicate the whole process of disease in clinical practice. For example, the dose of chemotherapy drug was calculated according to the average body surface, which varies in different individuals. Our study is focused on the analysis of patients with PD-L1 expression at CPS ≥10 and the survival data were not reported separately in patients with adenocarcinoma and squamous cell carcinoma in the KEYNOTE-181 trial. Therefore, we did not analyze the cost–effectiveness in patients with squamous cell carcinoma and patients with adenocarcinoma in the subgroup of patients with PD-L1 expression at CPS ≥10, respectively, which may lead to some bias. Second, utility scores had great influence on the results according to the sensitivity analysis. As the KEYNOTE-181 study did not publish the information, utilities applied in our study were based on the previously published literature. Additionally, subsequent treatments are not specified in the study and palliative symptomatic treatment is a recommended third-line therapy, as no drugs have

been demonstrated to be effective [30]. Therefore, we assume that patients in both groups accept basic support care when the disease progresses.

Conclusion

For patients with advanced EC whose PD-L1 CPS is ≥10, pembrolizumab is not a cost-effective second-line therapy versus standard chemotherapy at the current WTP of US$150,000 from the US payer perspective.

Summary points

- Metastatic esophageal cancer (EC) is a fatal disease, of which the prognosis is typically poor, with a median overall survival (OS) of less than a year.
- Anti-PD-1/PD-L1 treatments have shown significant tumor responses in patients with advanced EC.
- Pembrolizumab is a humanized, monoclonal anti-PD-1 antibody that has been proven to gain an obvious OS benefit with acceptable safety in patients with metastatic EC when the disease progresses during first-line therapies.
- The randomized phase III, open-label KEYNOTE-181 clinical trial demonstrated that pembrolizumab significantly prolonged OS and progression-free survival versus chemotherapy for advanced EC in patients with PD-L1 combined positive score (CPS) ≥10 as second-line therapy.
- Because pembrolizumab is expensive, it is still unknown whether the use of pembrolizumab for advanced EC would be a cost-effective option with patients whose PD-L1 CPS ≥10.
- We extracted the clinical data from the KEYNOTE-181 study and calculated the costs.
- The decision analysis Markov model was established to assess the cost–effectiveness of pembrolizumab versus chemotherapy as second-line therapy for advanced EC from the US payer perspective.
- Patients in the pembrolizumab group spent an additional US$184,786.36 and produced 0.35 QALYs more than the chemotherapy group, which resulted in an incremental cost–effectiveness ratio of US$527,961.03 per QALY.
- For patients with advanced EC whose PD-L1 CPS ≥10, pembrolizumab is not a cost-effective second-line therapy versus standard chemotherapy from the US payer perspective.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2021-0165

Author contributions

Conception and design: X Peng, Q Xie. Development of methodology: X Peng, Q Xie. Analysis and interpretation of data: Q Xie, Y Luo.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

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