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Cost-effectiveness analysis of penpulimab combined with paclitaxel and carboplatin as first-line treatment for metastatic squamous non-small-cell lung cancer in China

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ABSTRACT:

Objectives: Penpulimab is a novel programmed death (PD)-1 inhibitor that has been approved in China for use in combination with chemotherapy as a first-line treatment for locally advanced or metastatic squamous non-small-cell lung cancer (sq-NSCLC). However, the cost-effectiveness of this treatment in China remains to be determined. The objective of this study is to assess the cost-effectiveness of penpulimab combined with paclitaxel and carboplatin for metastatic sq-NSCLC.

Design: Based on the AK105-302 trial (ClinicalTrials.gov NCT03866993), a Markov model was created to evaluate the disease progression of metastatic sq-NSCLC patients over 10 years. The model included progression-free survival (PFS), disease progression (PD), and death. Quality-adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER) were calculated, and the robustness of the model's output was assessed by sensitivity studies.

Results: In comparison with chemotherapy group, the cost of penpulimab plus chemotherapy group increased by $3717.72 and QALYs increased by 0.43 QALYs. The incremental cost-utility ratio was $8625.78/QALYs, which meets the conditions well below the WTP threshold of $38052, with higher cost-effectiveness benefits, as confirmed by sensitivity analysis results.

Conclusions: Under the Chinese health system, penpulimab plus paclitaxel and carboplatin have a cost-effective in metastatic sq-NSCLC and can be used as an economical and effective treatment option.

Keywords: penpulimab, cost-effectiveness, sq-NSCLC, AK105-302, health economics

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study addressed the unmet need for economic evaluation of penpulimab, and for the first time evaluated the cost-effectiveness of penpulimab plus chemotherapy for metastatic sq-NSCLC in China.

⇒ A large, multicentre, randomised trial (AK105-302, NCT03866993) was used as the basis for this study.

⇒ Sensitivity analyses were used to explore the stability of the model to compare the effects of different factors on the study.

⇒ The long-term benefits remain an unresolved issue.

⇒ The health utility was derived from relevant literature which may have been unrepresented.

INTRODUCTION

In recent years, lung cancer has emerged as the most prevalent malignant tumour globally, exhibiting a rising incidence and mortality rate. The latest report by the International Agency for Research on Cancer (IARC) indicates that the global incidence of new lung cancer cases in 2022 reached 2.48 million, representing 12.4% of all new cancer cases worldwide, establishing lung cancer as the most prevalent form of cancer worldwide[1]. Approximately 80-85% of all lung cancers are non-small cell lung cancers (NSCLC)[2], with squamous histological subtypes accounting for nearly 25%[3]. Conventional platinum-based two-agent chemotherapy has historically constituted the standard therapeutic option for sq-NSCLC, but it has a low frequency of sensitive mutations and a poorer prognosis than adenocarcinoma[4] [5]. Consequently, the development of programmed death-(ligand) 1 (PD-(L)1) inhibitors provides more alternatives for sq-NSCLC.

A review of clinical studies has demonstrated the efficacy of PD-(L)1 inhibitors plus chemotherapy in prolonging the survival of sq-NSCLC patients[6-8]. In addition, the Chinese Society of Clinical Oncology's (CSCO) guidelines recommend that the first-line therapeutic option for metastatic sq-NSCLC is the use of PD-(L)1 inhibitors, either alone or in conjunction with chemotherapy[9]. Nevertheless, the relatively higher cost of imported PD-(L)1 inhibitors and the high cost of prophylaxis have somewhat limited the widespread use of this class of drugs, making the development of domestic PD-(L)1 inhibitors a matter of particular importance.

Penpulimab, a novel PD-1 inhibitor, was developed in China. It belongs to the IgG1 subtype of monoclonal antibodies and features a unique modification of the fragment crystal structure[10]. In January 2023, penpulimab was approved by the Chinese National Medical Products Administration (NMPA) in combination with paclitaxel and carboplatin for locally advanced or metastatic sq-NSCLC. The results of a clinical trial (AK105-302) evaluating the efficacy of penpulimab plus chemotherapy for metastatic sq-NSCLC were used to inform the relevant indication[11].The results demonstrated that

penpulimab plus chemotherapy exhibited a significant prolongation progression-free survival (PFS) of 3.4 months compared to chemotherapy group (7.6 months *vs* 4.2 months). Additionally, the risk of disease progression or death was reduced by 56%. Furthermore, the tolerability profile was favorable, and with a notable absence of a significant increase in adverse events (AEs) occurring during the period. Although penpulimab in combination with chemotherapy has demonstrated promising clinical benefits, the economic implications of its use in China remains uncertain. Therefore, this study aimed to examine the cost-effectiveness of penpulimab plus chemotherapy in Chinese metastatic sq-NSCLC patients.

METHODS

Target population and interventions

The target population of AK105-302 was locally advanced or metastatic sq-NSCLC patients in China. Participants were randomised (1:1) to receive penpulimab or placebo in combination with carboplatin (AUC 5 mg/ml/min) plus paclitaxel (175 mg/m^2) intravenously on day 1 of every 3 weeks for a total of four cycles, followed by penpulimab or placebo as maintenance therapy. We assumed that body surface area (1.72 m^2) and creatinine clearance (70 ml/min) [12 13].

Model Structure

Based on the AK105-302 trial, we developed a Markov model to analysis the cost-effectiveness of penpulimab plus paclitaxel and carboplatin as first-line treatment. Three main clinical states were defined: PFS, disease progression (PD) and death. The dosing regimen of the clinical trial was employed to define the cycle, which was set to 21 days. The duration of the trial was set to 10 years, with the assumption that all participants were in the PFS at the start of the model and that transitions between states were irreversible, as shown in the model in Figure 1. The main output metrics were the total cost and QALYs. The cost and QALYs were treated with a discount rate of 5% to evaluate the economy of the treatment scheme. According to the 2023 National

Economic and Social Development Statistics Bulletin[14], three times GDP per capita ($38,052 U.S. dollars) was set as the WTP threshold.

Transfer probability

The survival data were acquired from the AK105-302 trial using the Engauge Digitizer software, which was used to extract the raw survival curves of the two groups, reconstruct the individual data, and fit parameter distributions using R studio. The parameter distributions used in this study included Weibull, Exponential, Log-logistic, Log-normal, and Gompertz. The fitting distributions were identified by utilizing the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) values in conjunction with an examination of the fitted graph for each distribution. The relevant parameters are presented in Table 1.

Table1 KM curve optimum fitting distribution and parameters

Survival	Optimum fitting distribution	Fitting parameters			
		λ	γ	κ	η
PFS curve (penpulimab-combination group)	Weibull	0.0681	1.108		
PFS curve (placebo-combination group)	Log-logistic			2.790	4.592
OS curve (penpulimab-combination group)	Weibull	0.0252	1.318		
OS curve (placebo-combination group)	Log-logistic			1.674	19.474

Cost and Utility Values

In considering the Chinese healthcare system and the actual situation based on the AK105-302 clinical trial, we only considered the direct medical costs, including drug costs, medical management, routine follow-up, AEs and best supportive care costs. Drug prices were obtained from public databases[15]. Medical management costs included the cost of consultations, injections, hospitalization and nursing care, and were set at one visit per treatment cycle. After disease progression, chemotherapy group were transitioned to receive penpulimab monotherapy. The AK105-302 trial did not provide details on post-progression medications and ratios in the experimental group, and in accordance with the Clinical Guidelines for the Diagnosis and Treatment of Lung Cancer published by CSCO 2023[16], we assumed that the experimental group would receive second-line treatment after disease progression, including best supportive care and chemotherapy (Docetaxel). The costs obtained from the literature were adjusted to

2023 according to the growth rate of the Chinese Consumer Price Index for Healthcare and Personal Goods for each year. In accordance with the 2020 edition of the China Pharmacoeconomic Evaluation Guidelines[17], only AEs of grade ≥3 (incidence >5%) were included, assuming that each adverse effect occurred only once. Model inputs are tabulated below (Table 2).

Table 2 Model inputs

Parameters	Baseline value	Ranges		Distribution	Basis of variables	Source
		Lower	Upper			
Penpulimab per 200 mg	1008.85	706.19	1311.50	Gamma	±30%	Local charge
Paclitaxel price per 175 mg/m^2	94.67	66.27	123.07	Gamma	±30%	Local charge
Carboplatin price per 5.0 mg/ml/min	30.02	21.01	39.02	Gamma	±30%	Local charge
Docetaxel price per 75mg/m^2	27.34	19.14	35.54	Gamma	±30%	Local charge
Best supportive care/cycle	336.18	235.33	437.04	Gamma	±30%	[18]
Routine follow-up cost /cycle	118.37	82.86	153.88	Gamma	±30%	[19]
Medical service costs/cycle	13.69	9.58	17.80	Gamma	±30%	[19]
Neutrophil count decreased	126.39	88.48	164.31	Gamma	±30%	[19]
Anaemia	152.48	106.74	198.23	Gamma	±30%	[19]
White blood cell decreased	126.39	88.48	164.31	Gamma	±30%	[19]
Platelet count decreased	1654.97	1158.48	2151.46	Gamma	±30%	[19]
Utility						
Utility of progression-free survival	0.856	0.813	0.899	Beta	95%CI	[20]
Utility of disease progression	0.768	0.730	0.806	Beta	95%CI	[20]
Risk of AE						
Penpulimab plus chemotherapy group						
Neutrophil count decreased	0.45	0.32	0.59	Beta	±30%	[11]
White blood cell decreased	0.20	0.14	0.26	Beta	±30%	[11]
chemotherapy group						
Neutrophil count decreased	0.51	0.36	0.66	Beta	±30%	[11]
Anaemia	0.08	0.06	0.10	Beta	±30%	[11]
White blood cell decreased	0.21	0.15	0.27	Beta	±30%	[11]
Platelet count decreased	0.05	0.04	0.07	Beta	±30%	[11]
Others						
Discount rate	0.05	0.00	0.08	Fixed	-	[17]

Sensitivity analysis

To test the stability of each parameter change on our cost-effectiveness model, one-way deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were conducted. For the one-way DSA, PFS and PD status utility values were analyzed with reference to 95% confidence intervals of the literature data. Other costs

and the incidence of adverse events were analyzed with 30% of the basic value as the upper and lower limits, and the tornado diagram were used as the form of the output of the results. Second-order Monte Carlo simulations were performed with reference to the distribution form of each parameter. The results were illustrated graphically in the form of cost-effectiveness scatter plots and acceptable curves.

RESULTS

Base-case analysis

The results showed an increase in cost of $3717.72 and an increase in effectiveness of 0.43 QALYs for the penpulimab group compared to chemotherapy group alone, with an incremental cost-effectiveness ratio for both of $8625.78/QALYs (Table 3), which is well below the WTP threshold of $38052.

Table 3 Base-case results.

Group	Cost/$	Incremental costs	QALYs	Incremental QALYs	ICER ($/QALY)
chemotherapy	21117.32	-	1.75	-	-
penpulimab plus chemotherapy	24835.04	3717.72	2.18	0.43	8625.78

One-way deterministic sensitivity analysis

The one-way PSA for the penpulimab group and chemotherapy group was presented in Figure 2. The results showed that the main parameters affecting ICER were the discount rate and penpulimab cost, with the discount rate having the greatest impact on the results. As the relevant parameters moved up and down within the designated range, the ICER consistently remained below the set WTP threshold, thereby corroborating the findings of the base-case analysis and indicating that the model was relatively stable.

Probabilistic sensitivity analysis

The PSA scatter plot demonstrated the incremental cost and effect data resulting from 1,000 Monte Carlo simulations. As illustrated in Figure 3, the scatter plot demonstrated that the values were all below the WTP threshold in the first quadrant when WTP was

set at 1x GDP per capita. Furthermore, the acceptability curves demonstrated that the penpulimab group exhibited a pronounced advantage over the chemotherapy group at WTP thresholds spanning from $12,684/QALY to $38,052/QALY (1x to 3x GDP per capita), with a 100% probability of cost-effectiveness (Figure 4).

DISCUSSION

In AK105-302 clinical trial, penpulimab plus chemotherapy demonstrated significant advantages over chemotherapy alone for locally advanced or metastatic sq-NSCLC, with a prolongation of median survival by 3.4 months, a high 30-month overall survival rate of 51.6%, which was well tolerated. Based on this study, the NMPA approved penpulimab plus paclitaxel and carboplatin for the first-line treatment of locally advanced or metastatic sq-NSCLC. In 2021, penpulimab was approved for the treatment of relapsed or refractory classical Hodgkin's lymphoma in patients who had received at least two systemic chemotherapies[10 21]. This approval provides Chinese NSCLC and lymphoma patients with additional therapeutic options.

As the fifth domestically produced PD-1 inhibitor, penpulimab has demonstrated promising clinical efficacy and safety. However, pharmacoeconomic evidence of its cost-effectiveness remains to be explored. This study addressed the unmet need for economic evaluation of penpulimab, and for the first time evaluated the cost-effectiveness of penpulimab plus chemotherapy for metastatic sq-NSCLC in China. Base-case analysis indicated that penpulimab group resulted in a greater number of QALYs, although this was accompanied by a corresponding increase in cost. The ICER was $8,625.78/QALYs in comparison to the chemotherapy group, which was well below the WTP of $38,052. The sensitivity analysis indicated that the cost-effectiveness of penpulimab group was likely to be nearly 100% at this threshold level.

In recent years, the state has actively promoted the development and application of domestically produced anticancer drugs. This initiative, coupled with a national drug

price negotiation system, has resulted in a notable reduction in drug costs[22]. These measures have facilitated a gradual increase in the utilization of domestically manufactured anticancer drugs in the Chinese market, offering significant benefits to cancer patients in the country. Currently, penpulimab in combination with chemotherapy is not included in the National Reimbursement Database for metastatic sq-NSCLC. However, the economic results indicated that it offers better cost-effectiveness advantages. It is anticipated that these advantages will become more pronounced once it is covered by health insurance. This provides evidence to support the wider use of domestically manufactured anticancer drugs.

However, there are some limitations of this study. Firstly, the health utility values have not been published in the results of the AK105-302 study, we chosed to refer to data from relevant Chinese NSCLC patients, which may introduce some bias into the results. Furthermore, the long-term benefits of penpulimab plus chemotherapy for sq-NSCLC remains an unresolved issue. The model estimated subsequent treatment and long-term efficacy. However, the extrapolation of data in the study could introduce bias by over- or underestimating long-term survival outcomes. Thirdly, we did not consider grades 1 or 2 AEs. Despite these being relatively mild, they still have an impact on the total cost. Fourthly, potential changes in clinical efficacy of penpulimab plus chemotherapy in comparison to chemotherapy alone for sq-NSCLC stratified by PD-L1 tumors proportion score were not considered in this study, and more detailed subgroup data will be collected to explore the economic benefits. Despite these limitations, the conclusions of the sensitivity analyses corroborate the base-case analysis that penpulimab plus chemotherapy represents a cost-effective treatment.

CONCLUSION

In summary, penpulimab plus chemotherapy proves to be more cost-effective than chemotherapy alone for metastatic sq-NSCLC. Furthermore, it represents a viable treatment option that is also cost-effective within the Chinese healthcare system.

Contributors: LW, NL and YG were involved in study conceptualization. LW and NL completed the data collection and analysis. LW wrote and edited the draft. XH provided the related resources and method. RD is responsible for the overall content as the guarantor. All authors approved the final manuscript.

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Patient consent for publication: Not applicable.

Provenance and peer review: Not commissioned; externally peer reviewed

Data availability statement: All data relevant to the study are included in the article or uploaded as online supplemental information

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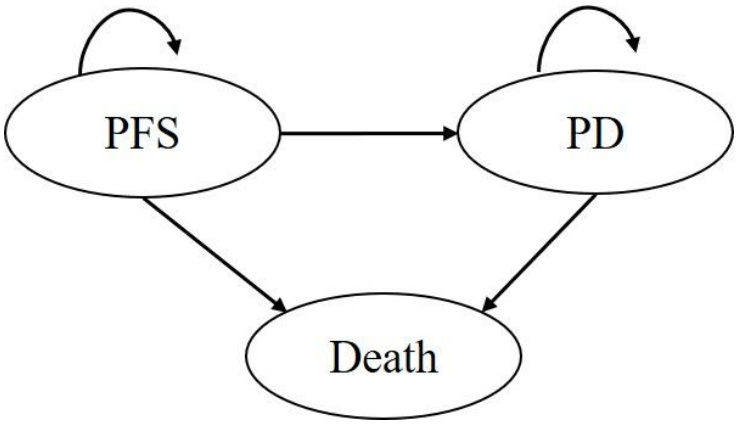

Figure 1 Markov models

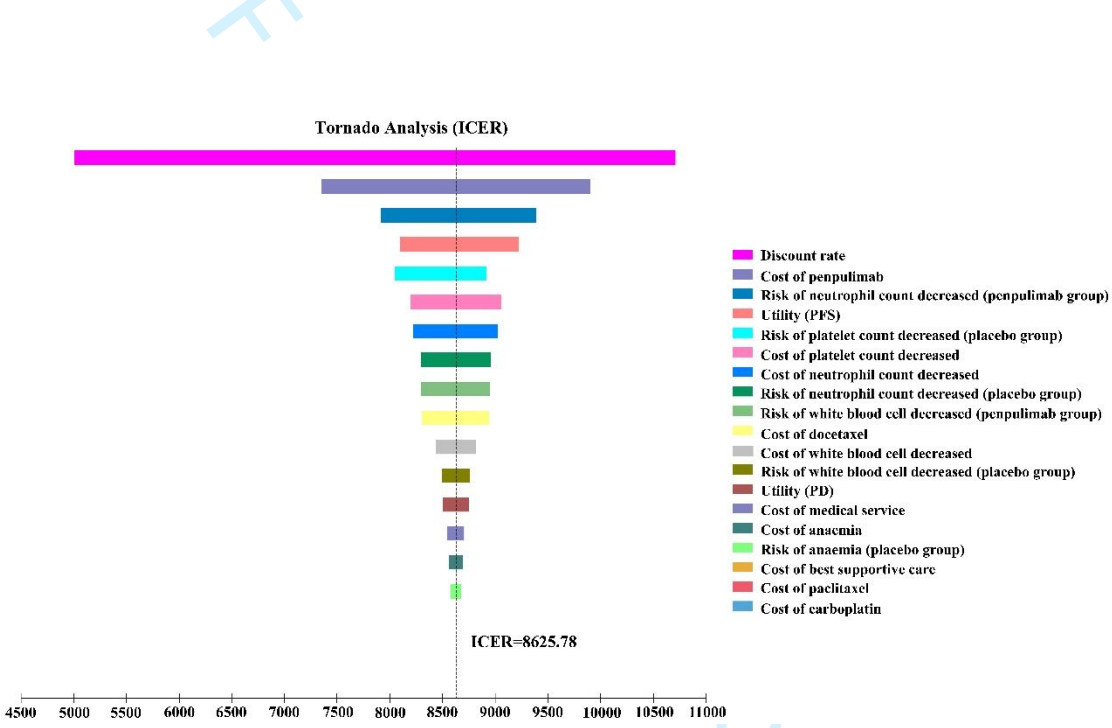

Figure 2 Tornado Analysis of penpulimab plus chemotherapy vs. chemotherapy.

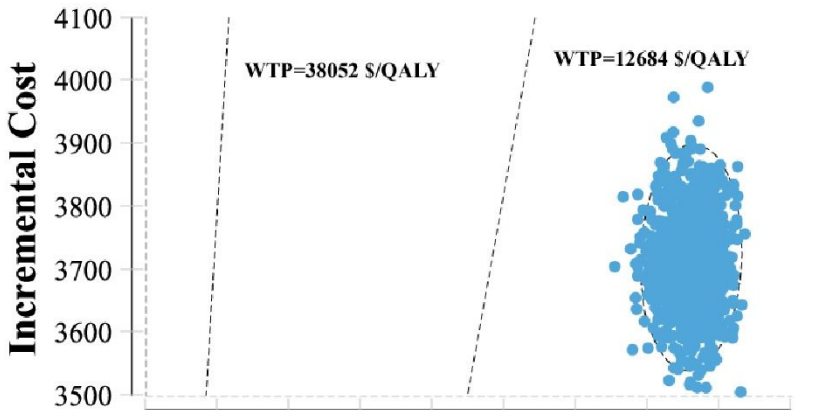

Figure 3 The scatter plot diagram showed the probability at the current WTP threshold.

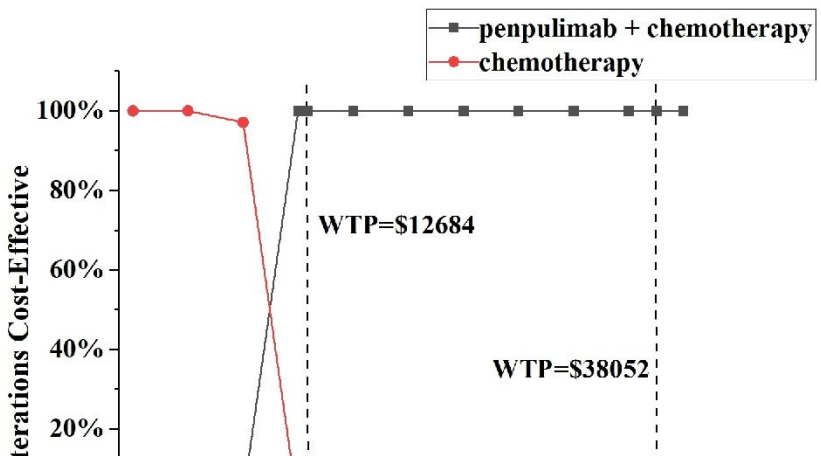

Figure 4 Cost-effectiveness acceptability curves for penpulimab plus chemotherapy vs. chemotherapy.

Supplemental table

AIC and BIC values of different K-M curve fitting distributions

	Group	Survival curve	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
AIC	penpulimab+chemotherapy	iDFS	844.2596	844.4775	844.3246	820.5727	823.8946
		OS	665.0947	661.4978	663.1322	663.6693	661.7181
	placebo+ chemotherapy	iDFS	836.3011	816.5411	838.3007	764.1781	745.8202
		OS	840.7221	831.6527	836.2086	837.0231	831.0435
BIC	penpulimab+chemotherapy	iDFS	847.4244	850.8071	850.6542	826.9022	830.2242
		OS	668.2595	667.8274	669.4618	669.9988	668.0477
	placebo+ chemotherapy	iDFS	839.4659	822.8707	844.6303	770.5077	752.1498
		OS	843.8869	837.9823	842.5382	843.3527	837.3731

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Cost-effectiveness analysis of penpulimab combined with paclitaxel and carboplatin as first-line treatment for metastatic squamous non-small-cell lung cancer in China

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ABSTRACT:

Objectives: Penpulimab is a novel programmed death (PD)-1 inhibitor that has been approved in China for use in combination with chemotherapy as a first-line treatment for locally advanced or metastatic squamous non-small-cell lung cancer (sq-NSCLC). However, the cost-effectiveness of this treatment in China remains to be determined. The objective of this study is to assess the cost-effectiveness of penpulimab combined with paclitaxel and carboplatin for metastatic sq-NSCLC.

Design: Based on the AK105-302 trial (ClinicalTrials.gov NCT03866993)**,** a Markov model was created to evaluate the disease progression of metastatic sq-NSCLC patients over 10 years. The model included progression-free survival (PFS), disease progression (PD), and death. Quality-adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER) were calculated, and sensitivity studies assessed the robustness of the model's output.

Results: In comparison with the chemotherapy group, the cost of penpulimab plus chemotherapy group increased by $3717.72 and QALYs increased by 0.43 QALYs. The ICER was $8625.78/QALY, which meets the conditions well below the WTP threshold of $38052, with higher cost-effectiveness benefits, as confirmed by sensitivity analysis results.

Conclusions: Under the Chinese health system, penpulimab plus paclitaxel and carboplatin is cost-effective in metastatic sq-NSCLC and can be used as an economical and effective treatment option.

Keywords: penpulimab, cost-effectiveness, sq-NSCLC, AK105-302, health economics

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study developed an economic evaluation from the perspective of the Chinese healthcare system using a Markov model to evaluate the cost-effectiveness of penpulimab combined with paclitaxel and carboplatin for metastatic sq-NSCLC.

⇒ A large, multicentre, randomised trial (AK105-302, NCT03866993) was used as the basis for this study.

⇒ Sensitivity analyses were used to explore the stability of the model and compare the effects of different factors on the study.

⇒ The long-term benefits remain an unresolved issue.

⇒ The health utility was derived from relevant literature which may have been unrepresented.

INTRODUCTION

In recent years, lung cancer has emerged as the most prevalent malignant tumor globally, exhibiting a rising incidence and mortality rate. The latest report by the International Agency for Research on Cancer (IARC) indicates that the global incidence of new lung cancer cases in 2022 reached 2.48 million, representing 12.4% of all new cancer cases worldwide, establishing lung cancer as the most prevalent form of cancer worldwide[1]. Approximately 80-85% of all lung cancers are non-small cell lung cancers (NSCLC)[2], with squamous histological subtypes accounting for nearly 25%[3]. Conventional platinum-based two-agent chemotherapy has historically constituted the standard therapeutic option for sq-NSCLC, but it has a low frequency of sensitive mutations and a poorer prognosis than adenocarcinoma[4] [5]. Consequently, the development of programmed death-(ligand) 1 (PD-(L)1) inhibitors provides more alternatives for sq-NSCLC.

A review of clinical studies has demonstrated the efficacy of PD-(L)1 inhibitor plus chemotherapy in prolonging the survival of sq-NSCLC patients[6-8]. In addition, the Chinese Society of Clinical Oncology's (CSCO) guidelines recommend that the first-line therapeutic option for metastatic sq-NSCLC is the use of PD-(L)1 inhibitors, either alone or in conjunction with chemotherapy[9]. Nevertheless, the relatively higher cost of imported PD-(L)1 inhibitors and the high cost of prophylaxis have somewhat limited the widespread use of this class of drugs, making the development of domestic PD-(L)1 inhibitors a matter of particular importance.

Penpulimab, a novel PD-1 inhibitor, was developed in China. It belongs to the IgG1 subtype of monoclonal antibodies and features a unique modification of the fragment crystal structure[10]. In January 2023, penpulimab was approved by the Chinese National Medical Products Administration (NMPA) in combination with paclitaxel and carboplatin for locally advanced or metastatic sq-NSCLC. The results of a clinical trial (AK105-302) evaluating the efficacy of penpulimab plus chemotherapy for metastatic sq-NSCLC were used to inform the relevant indication[11].The results demonstrated that

penpulimab plus chemotherapy exhibited a significant prolongation progression-free survival (PFS) of 3.4 months compared to the chemotherapy group (7.6 months *vs* 4.2 months). Additionally, the risk of disease progression or death was reduced by 56%. Furthermore, the tolerability profile was favorable with a notable absence of a significant increase in adverse events (AEs) occurring during the period. Although penpulimab in combination with chemotherapy has demonstrated promising clinical benefits, the economic implications of its use in China remain uncertain. Therefore, this study aimed to examine the cost-effectiveness of penpulimab plus chemotherapy in Chinese metastatic sq-NSCLC patients.

METHODS

Target population and interventions

The target population of AK105-302 was locally advanced or metastatic sq-NSCLC patients in China. Participants were randomized (1:1) to receive penpulimab or placebo in combination with carboplatin (AUC 5 mg/ml/min) plus paclitaxel (175 mg/m^2) intravenously on day 1 of every 3 weeks for a total of four cycles, followed by penpulimab or placebo as maintenance therapy. We assumed a body surface area of 1.72 m² and a creatinine clearance of 70 mL/min[12 13].

Model Structure

Based on the AK105-302 trial, we developed a Markov model to analyze the cost-effectiveness of penpulimab plus paclitaxel and carboplatin as first-line treatment. Three main clinical states were identified: PFS, disease progression (PD), and death. The dosing regimen of the clinical trial was employed to define the cycle, which was set to 21 days. The duration of the trial was set to 10 years, with the assumption that all participants were in the PFS at the start of the model and that transitions between states were irreversible, as shown in the model in Figure 1. The main output metrics were the total cost and QALYs. The cost and QALYs were treated with a discount rate of 5% to evaluate the economy of the treatment scheme. According to the 2023 National

Economic and Social Development Statistics Bulletin[14], three times GDP per capita ($38,052 U.S. dollars) was set as the WTP threshold.

Transfer probability

The survival data were acquired from the AK105-302 trial using the Engauge Digitizer software, which was used to extract the raw survival curves of the two groups, reconstruct the individual data, and fit parameter distributions using R studio. The parameter distributions used in this study included Weibull, Exponential, Log-logistic, Log-normal, and Gompertz. The fitting distributions were identified by utilizing the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) values in conjunction with an examination of the fitted graph for each distribution. The AIC and BIC values of the fitting model are shown in the Supplemental Table. The relevant parameters are presented in Table 1.

Table 1 KM curve optimum fitting distribution and parameters

Survival	Optimum fitting distribution	Fitting parameters			
		λ	γ	κ	η
PFS curve (penpulimab-combination group)	Weibull	0.0681 (0.0647-0.0715)	1.108 (1.053-1.164)		
PFS curve (placebo-combination group)	Log-logistic			2.790 (2.651-2.930)	4.592 (4.362-4.822)
OS curve (penpulimab-combination group)	Weibull	0.0252 (0.0239-0.0264)	1.318 (1.252-1.384)		
OS curve (placebo-combination group)	Log-logistic			1.674 (1.590-1.758)	19.474 (18.500-20.448)

Cost and Utility Values

In considering the Chinese healthcare system and the actual situation based on the AK105-302 clinical trial, we only considered the direct medical costs, including drug costs, medical management, routine follow-up, AEs, and best supportive care costs. Drug prices were obtained from public databases[15]. Medical management costs included the cost of consultations, injections, hospitalization and nursing care, and were set at one visit per treatment cycle. After disease progression, the chemotherapy group was transitioned to receive penpulimab monotherapy. The AK105-302 trial did not provide details on post-progression medications and ratios in the experimental group under the Clinical Guidelines for the Diagnosis and Treatment of Lung Cancer

published by CSCO 2023[16], we assumed that the experimental group would receive second-line treatment after disease progression, including best supportive care and chemotherapy (Docetaxel). The costs obtained from the literature were adjusted to 2023 based on the annual growth rate of the Chinese Consumer Price Index for Healthcare and Personal Goods. In accordance with the 2020 edition of the China Pharmacoeconomic Evaluation Guidelines[17], only AEs of grade ≥3 (incidence >5%) were included, assuming that each adverse effect occurred only once. Model inputs are tabulated below (Table 2).

Table 2 Model inputs

Parameters	Baseline value	Ranges		Distribution	Basis of variables	Source
		Lower	Upper			
Penpulimab per 200 mg	1008.85	706.19	1311.50	Gamma	±30%	Local charge
Paclitaxel price per 175 mg/m^2	94.67	66.27	123.07	Gamma	±30%	Local charge
Carboplatin price per 5.0 mg/ml/min	30.02	21.01	39.02	Gamma	±30%	Local charge
Docetaxel price per 75mg/m^2	27.34	19.14	35.54	Gamma	±30%	Local charge
Best supportive care/cycle	336.18	235.33	437.04	Gamma	±30%	[18]
Routine follow-up cost /cycle	118.37	82.86	153.88	Gamma	±30%	[19]
Medical service costs/cycle	13.69	9.58	17.80	Gamma	±30%	[19]
Neutrophil count decreased	126.39	88.48	164.31	Gamma	±30%	[19]
Anaemia	152.48	106.74	198.23	Gamma	±30%	[19]
White blood cell decreased	126.39	88.48	164.31	Gamma	±30%	[19]
Platelet count decreased	1654.97	1158.48	2151.46	Gamma	±30%	[19]
Utility						
Utility of progression-free survival	0.856	0.813	0.899	Beta	95%CI	[20]
Utility of disease progression	0.768	0.730	0.806	Beta	95%CI	[20]
Disutility						
Neutrophil count decreased	0.20	0.14	0.26	Beta	±30%	[21]
Anaemia	0.07	0.05	0.09	Beta	±30%	[21]
White blood cell decreased	0.20	0.14	0.26	Beta	±30%	[21]
Platelet count decreased	0.11	0.08	0.14	Beta	±30%	[21]
Risk of AE						
Penpulimab plus chemotherapy group						
Neutrophil count decreased	0.45	0.32	0.59	Beta	±30%	[11]
White blood cell decreased	0.20	0.14	0.26	Beta	±30%	[11]
chemotherapy group						
Neutrophil count decreased	0.51	0.36	0.66	Beta	±30%	[11]
Anaemia	0.08	0.06	0.10	Beta	±30%	[11]
White blood cell decreased	0.21	0.15	0.27	Beta	±30%	[11]
Platelet count decreased	0.05	0.04	0.07	Beta	±30%	[11]
Others						
Discount rate	0.05	0.00	0.08	Fixed	-	[17]

Sensitivity analysis

To test the stability of each parameter change on our cost-effectiveness model, one-way deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were conducted. For the one-way DSA, PFS and PD status utility values were analyzed concerning 95% confidence intervals of the literature data. Other costs and the incidence of adverse events were analyzed with 30% of the basic value as the upper and lower limits, and the tornado diagram was used as the form of the output of the results. Second-order Monte Carlo simulations were performed regarding the distribution form of each parameter. The results were graphically illustrated using cost-effectiveness scatter plots and acceptability curves.

Scenario analysis

Considering that penpulimab had not yet been listed on the National Health Insurance Drug List (NRDL) in metastatic sq-NSCLC, we assumed that the price of penpulimab floated between 0.5 times and 2 times in the NRDL.

RESULTS

Base-case analysis

The results showed an increase in the cost of $3717.72 and an increase in the effectiveness of 0.43 QALYs for the penpulimab group compared to the chemotherapy group alone, with an ICER for both of $8625.78/QALY (Table 3), which is well below the WTP threshold of $38052/QALY.

Table 3 Base-case results.

Group	Cost/$	Incremental costs	QALYs	Incremental QALYs	ICER ($/QALY)
chemotherapy	21117.32	-	1.73	-	-
penpulimab plus chemotherapy	24835.04	3717.72	2.16	0.43	8625.78

One-way deterministic sensitivity analysis

The one-way PSA for the penpulimab group and chemotherapy group was presented in Figure 2. The results showed that the main parameters affecting ICER were the

discount rate and penpulimab cost, with the discount rate having the greatest impact on the results. As the relevant parameters moved up and down within the designated range, the ICER consistently remained below the set WTP threshold, thereby corroborating the findings of the base-case analysis and indicating that the model was relatively stable.

Probabilistic sensitivity analysis

The PSA scatter plot illustrated the incremental cost and effect data derived from 1,000 Monte Carlo simulations. As illustrated in Figure 3, the scatter plot demonstrated that the values were all below the WTP threshold in the first quadrant when WTP was set at 1x GDP per capita. Furthermore, the acceptability curves demonstrated that the penpulimab group exhibited a pronounced advantage over the chemotherapy group at WTP thresholds spanning from $12,684/QALY to $38,052/QALY (1x to 3x GDP per capita), with a 100% probability of cost-effectiveness (Figure 4).

Scenario analysis

Figure 5 illustrated the impact of penpulimab cost on ICER. As the cost of penpulimab varied between $252 and $1,008 (0.5 to 2 times the current price), the ICER increased as the cost of penpulimab increased, and the ICER was all below the WTP threshold ($38,052/QALY).

DISCUSSION

In the AK105-302 clinical trial, penpulimab plus chemotherapy demonstrated significant advantages over chemotherapy alone for locally advanced or metastatic sq-NSCLC, with a prolongation of median survival by 3.4 months, a high 30-month overall survival rate of 51.6%, which was well tolerated. Based on this study, the NMPA has approved penpulimab plus paclitaxel and carboplatin for the first-line treatment of locally advanced or metastatic sq-NSCLC. In 2021, penpulimab was approved for the treatment of relapsed or refractory classical Hodgkin's lymphoma in patients who had received at least two systemic chemotherapies[10 22]. This approval provides Chinese

NSCLC and lymphoma patients with additional therapeutic options.

As the fifth domestically produced PD-1 inhibitor, penpulimab has demonstrated promising clinical efficacy and safety. However, pharmacoeconomic evidence of its cost-effectiveness remains to be explored. This study addressed the unmet need for economic evaluation of penpulimab, and for the first time evaluated the cost-effectiveness of penpulimab plus chemotherapy for metastatic sq-NSCLC in China. Base-case analysis indicated that penpulimab group resulted in a greater number of QALYs, although this was accompanied by a corresponding increase in cost. The ICER was $8,625.78/QALY in comparison to the chemotherapy group, which was well below the WTP of $38,052/QALY. The sensitivity analysis indicated that the cost-effectiveness of penpulimab group was likely to be nearly 100% at this threshold level.

In recent years, the state has actively promoted the development and application of domestically produced anticancer drugs. This initiative, coupled with a national drug price negotiation system, has resulted in a notable reduction in drug costs[23]. These measures have facilitated a gradual increase in the utilization of domestically manufactured anticancer drugs in the Chinese market, offering significant benefits to cancer patients in the country. Currently, penpulimab in combination with chemotherapy is not included in the National Reimbursement Database for metastatic sq-NSCLC. Therefore, we considered a broad price range for penpulimab to provide a rough assessment of the acceptability of treatment access for patients. The results showed that ICER increased positively with rising penpulimab costs, all below the WTP threshold. Overall, the economic results indicated that it offers better cost-effectiveness advantages. It is anticipated that these advantages will become more pronounced once it is covered by health insurance. This provides evidence to support the wider use of domestically manufactured anticancer drugs.

However, there are some limitations of this study. Firstly, the health utility values have not been published in the results of the AK105-302 study, we choose to refer to data from relevant Chinese NSCLC patients, which may introduce some bias into the results. Furthermore, the long-term benefits of penpulimab plus chemotherapy for sq-

NSCLC remain an unresolved issue. The model estimated subsequent treatment and long-term efficacy. However, the extrapolation of data in the study could introduce bias by over- or underestimating long-term survival outcomes. Thirdly, we did not consider grades 1 or 2 AEs. Despite these being relatively mild, they still have an impact on the total cost. Fourthly, potential changes in the clinical efficacy of penpulimab plus chemotherapy in comparison to chemotherapy alone for sq-NSCLC stratified by PD-L1 tumors proportion score were not considered in this study, and more detailed subgroup data will be collected to explore the economic benefits. Lastly, the research perspective, modeling approach, and selection of parameter inputs may also influence the generalizability of penpulimab cost-effectiveness analysis. Despite these limitations, the conclusions of the sensitivity analyses corroborate the base-case analysis that penpulimab plus chemotherapy represents a cost-effective treatment in China.

CONCLUSION

In summary, penpulimab plus chemotherapy proves to be more cost-effective than chemotherapy alone for metastatic sq-NSCLC. Furthermore, it represents a viable treatment option that is also cost-effective within the Chinese healthcare system.

Contributors: LW, NL, CY and YG were involved in study conceptualization. LW and NL completed the data collection and analysis. LW wrote and edited the draft. XH provided the related resources and method. RD is responsible for the overall content as the guarantor. All authors approved the final manuscript.

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Patient consent for publication: Not applicable.

Provenance and peer review: Not commissioned; externally peer reviewed

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Figure 1 Markov models.

Figure 2 Tornado Analysis of penpulimab plus chemotherapy vs. chemotherapy.

Figure 3 The scatter plot diagram showed the probability at the current WTP threshold.

Figure 4 Cost-effectiveness acceptability curves for penpulimab plus chemotherapy vs. chemotherapy.

Figure 5. Results of scenario analysis.

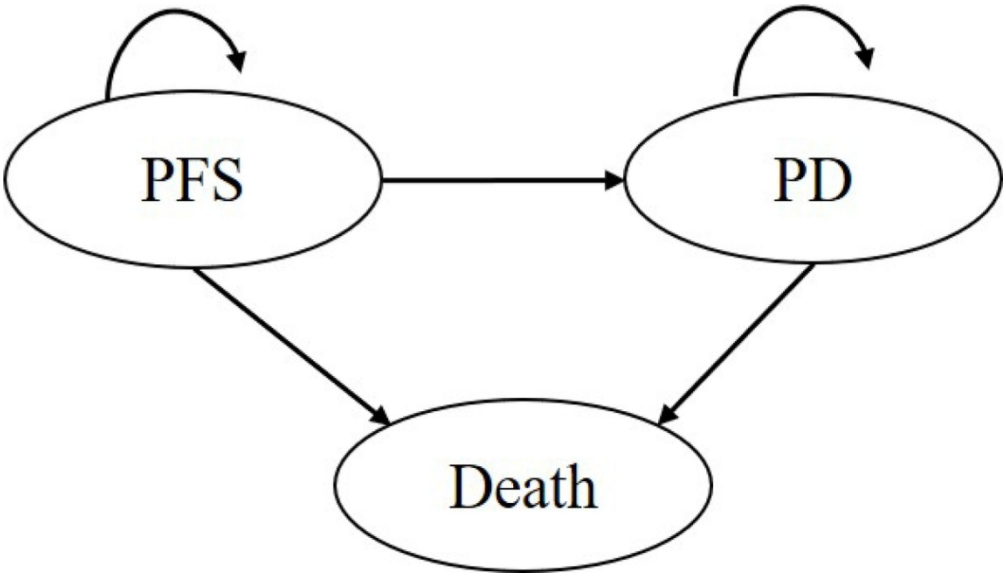

Figure 1 Markov models.

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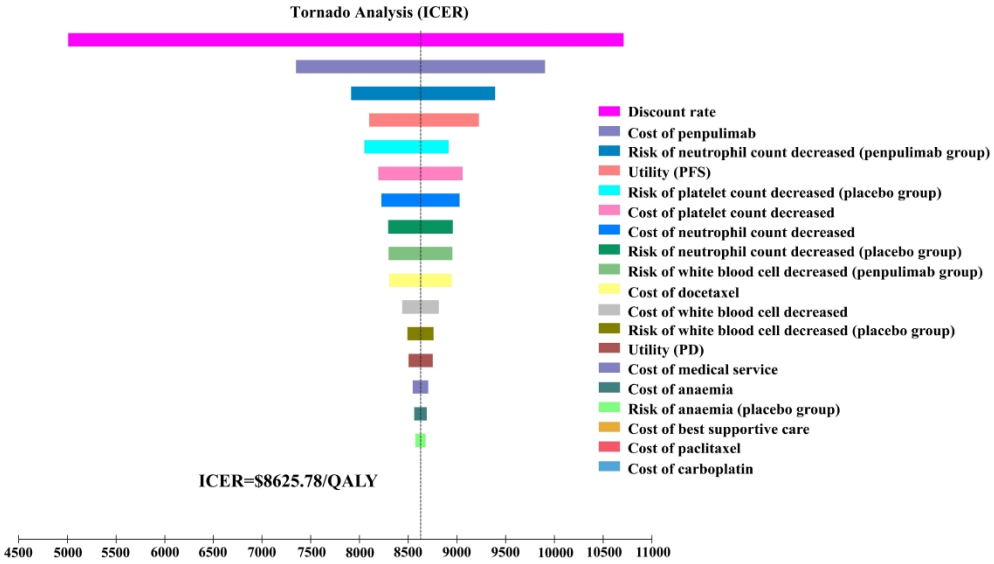

Figure 2 Tornado Analysis of penpulimab plus chemotherapy vs. chemotherapy.

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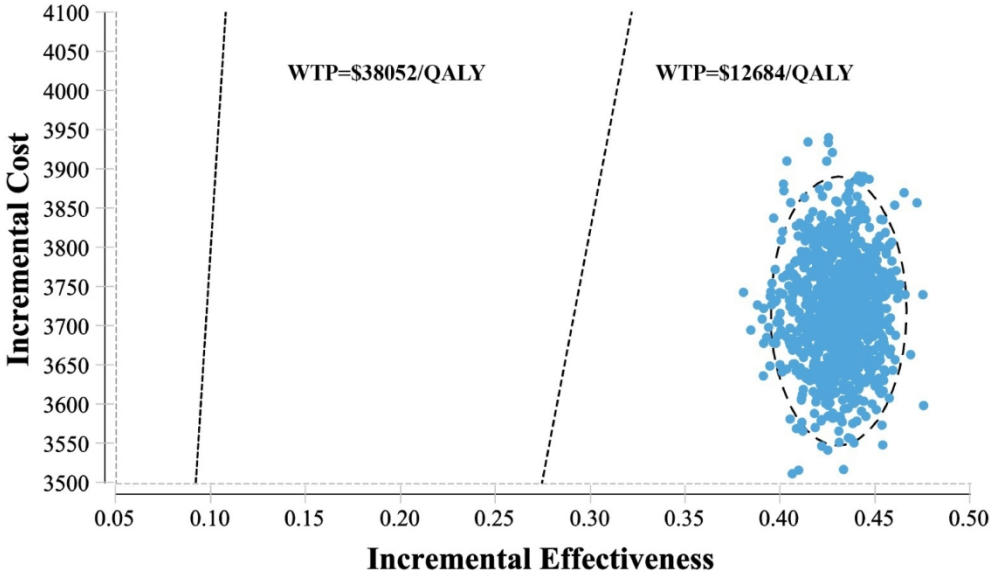

Figure 3 The scatter plot diagram showed the probability at the current WTP threshold.

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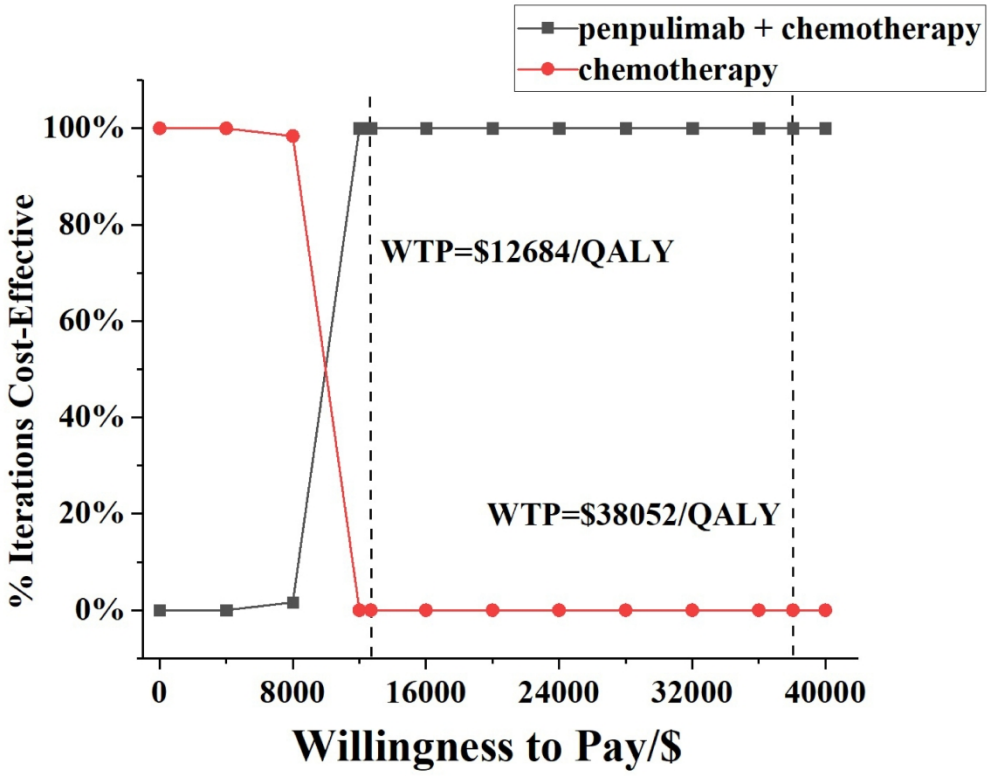

Figure 4 Cost-effectiveness acceptability curves for penpulimab plus chemotherapy vs. chemotherapy.

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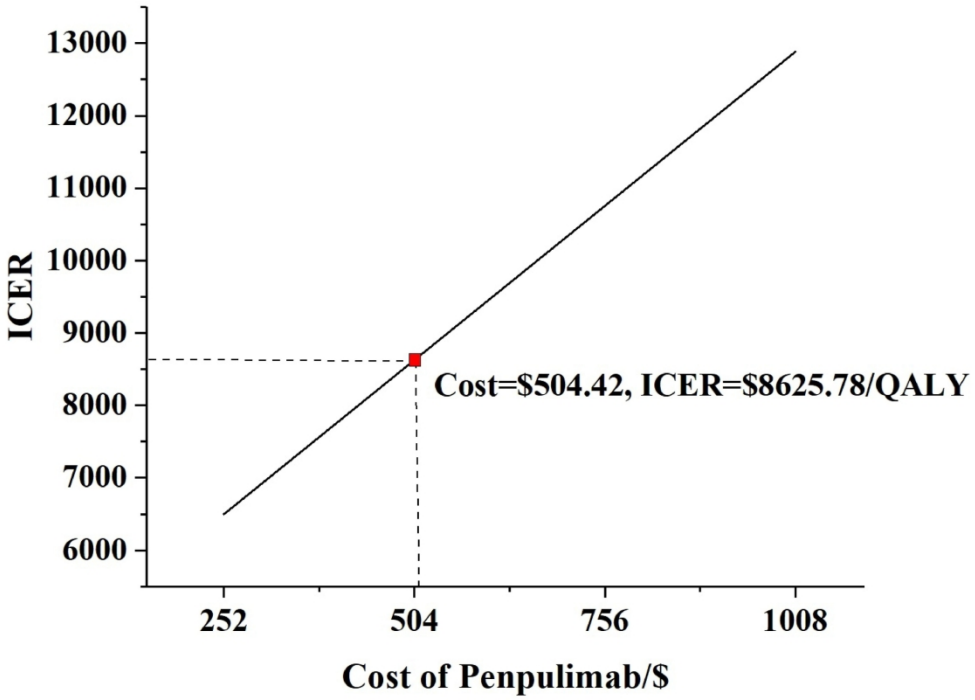

Figure 5. Results of scenario analysis.

186x143mm (300 x 300 DPI)

Table

AIC and BIC values of different K-M curve fitting distributions

	Group	Survival curve	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
AIC	penpulimab+chemotherapy	PFS	844.2596	844.4775	844.3246	820.5727	823.8946
		OS	665.0947	661.4978	663.1322	663.6693	661.7181
	placebo+ chemotherapy	PFS	836.3011	816.5411	838.3007	764.1781	745.8202
		OS	840.7221	831.6527	836.2086	837.0231	831.0435
BIC	penpulimab+chemotherapy	PFS	847.4244	850.8071	850.6542	826.9022	830.2242
		OS	668.2595	667.8274	669.4618	669.9988	668.0477
	placebo+ chemotherapy	PFS	839.4659	822.8707	844.6303	770.5077	752.1498
		OS	843.8869	837.9823	842.5382	843.3527	837.3731

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Cost-effectiveness analysis of penpulimab combined with paclitaxel and carboplatin as a first-line treatment for metastatic squamous non-small cell lung cancer in China

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ABSTRACT

Objectives: Penpulimab is a novel programmed death-1 (PD-1) inhibitor that has been approved in China for use in combination with chemotherapy as a first-line treatment for locally advanced or metastatic squamous non-small cell lung cancer (sq-NSCLC). However, the cost-effectiveness of this treatment in China remains to be determined. In this study, we aimed to assess the cost-effectiveness of penpulimab combined with paclitaxel and carboplatin for metastatic sq-NSCLC.

Design: Based on the AK105-302 trial (ClinicalTrials.gov NCT03866993), a Markov model was created to evaluate the disease progression of metastatic sq-NSCLC patients over 10 years. The model included progression-free survival, progressive disease, and death. The utility values were derived from published literature. Sensitivity studies were used to assess the robustness of the model outputs.

Setting: The Chinese healthcare system perspective.

Participants: A hypothetical Chinese cohort of patients with locally advanced or metastatic sq-NSCLC.

Interventions: Penpulimab plus chemotherapy versus chemotherapy.

Primary outcome measure: Costs, Quality-adjusted life years (QALYs), incremental cost-effectiveness ratio (ICER).

Results: Compared with the chemotherapy alone group, the cost of penpulimab plus chemotherapy increased by $3,717.72, with an increase of 0.43 QALYs. The ICER was $8,625.78/QALY, which was well below the willingness-to-pay threshold of $38,052/QALY. This demonstrated higher cost-effectiveness benefits, as confirmed by the sensitivity analysis results.

Conclusions: Under the Chinese health system, penpulimab plus paclitaxel and carboplatin is cost-effective for metastatic sq-NSCLC patients and can be used as an economical and effective treatment option.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study used a Markov model to evaluate the cost-effectiveness of penpulimab combined with paclitaxel and carboplatin for metastatic sq-NSCLC from the perspective of the Chinese healthcare system.

⇒ A large, multicenter, randomized clinical trial (AK105-302, NCT03866993) was used as the basis for this study.

⇒ Sensitivity analyses were used to explore the stability of the model and compare the effects of different factors on the outcomes.

⇒ The long-term benefits of this treatment remain to be explored.

⇒ The health utility values were derived from relevant literature, which may have been unrepresented.

INTRODUCTION

In recent years, lung cancer has emerged as the most prevalent malignant tumor type globally, with an increasing incidence and mortality rate. The latest report by the International Agency for Research on Cancer (IARC) has indicated that the global incidence of new lung cancer cases in 2022 reached 2.48 million, representing 12.4% of all new cancer cases and establishing lung cancer as the most prevalent cancer type worldwide[1]. Approximately 80-85% of all lung cancer cases are non-small cell lung cancer (NSCLC)[2], with squamous histological subtypes accounting for nearly 25%[3]. Conventional platinum-based two-agent chemotherapy has historically been the standard therapeutic option for squamous NSCLC (sq-NSCLC) patients. However, this subtype has a low frequency of sensitive mutations and poorer prognosis than lung adenocarcinoma[4 5]. Consequently, the development of programmed death-1 (PD-1) and PD-ligand 1 (PD-L1) inhibitors has provided alternative approaches for treating sq-NSCLC.

A review of clinical studies has demonstrated the efficacy of using a PD-1/PD-L1 inhibitor plus chemotherapy to prolong sq-NSCLC patient survival[6-8]. In addition, the Chinese Society of Clinical Oncology (CSCO) guidelines recommend that the first-line therapeutic option for metastatic sq-NSCLC be PD-1/PD-L1 inhibitors, either alone or in combination with chemotherapy[9]. Nevertheless, the relatively higher cost of imported PD-1/PD-L1 inhibitors and high cost of prophylaxis have somewhat limited the widespread use of this class of drugs, emphasizing the importance of developing domestic PD-1/PD-L1 inhibitors.

Penpulimab, a novel PD-1 inhibitor that was developed in China, belongs to the IgG1 subtype of monoclonal antibodies and features a uniquely modified fragment crystal structure[10]. In January 2023, penpulimab was approved by the Chinese National Medical Products Administration (NMPA) in combination with paclitaxel and carboplatin for locally advanced or metastatic sq-NSCLC. The results of a clinical trial (AK105-302) evaluating the efficacy of penpulimab plus chemotherapy for metastatic

sq-NSCLC were used to inform the relevant indication[11]. The results demonstrated that penpulimab plus chemotherapy treatment significantly prolonged the progression-free survival (PFS) of patients compared with the chemotherapy alone group (7.6 months *vs*. 4.2 months, respectively). Additionally, the risk of disease progression or death was reduced by 56%. Furthermore, the treatment had a favorable tolerability profile, with no significant increase in adverse events (AEs) occurring during the trial period. Although penpulimab in combination with chemotherapy has demonstrated promising clinical benefits, the economic implications of its use in China remain uncertain. Therefore, in this study, we aimed to examine the cost-effectiveness of penpulimab plus chemotherapy in Chinese metastatic sq-NSCLC patients.

METHODS

Target population and interventions

The target population of AK105-302 was locally advanced or metastatic sq-NSCLC patients in China. Participants were randomized (1:1) to receive penpulimab or placebo in combination with carboplatin (AUC 5 mg/mL/min) plus paclitaxel (175 mg/m^2) intravenously on day 1 of every 3 weeks for a total of four cycles, followed by penpulimab or placebo as maintenance therapy. We assumed a body surface area of 1.72 m^2 and creatinine clearance rate of 70 mL/min[12 13].

Model structure

Using the AK105-302 trial, we developed a Markov model to analyze the cost-effectiveness of penpulimab plus paclitaxel and carboplatin as first-line treatment. Three main clinical states were identified: PFS, progressive disease (PD), and death. The dosing regimen of the clinical trial was employed to define the cycle, which was 21 days. The duration of the trial was set to 10 years, with the assumptions that all participants were in the PFS state at the start of the model and transitions between states were irreversible, as shown in Figure 1. The main output metrics were the total cost and quality-adjusted life years (QALYs), with a discount rate of 5% applied to evaluate the

economy of the treatment scheme. According to the 2023 National Economic and Social Development Statistics Bulletin[14], three times gross domestic product (GDP) per capita ($38,052 U.S. dollars) was set as the willingness-to-pay (WTP) threshold.

Transfer probability

The survival data were acquired from the AK105-302 trial with the Engauge Digitizer software, which was used to extract the raw survival curves of the two groups, reconstruct the individual data, and fit parameter distributions using R studio. The parameter distributions used in this study included Weibull, Exponential, Log-logistic, Log-normal, and Gompertz. The fitting distributions were identified using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values in conjunction with examining the fitted graph for each distribution. The AIC and BIC values of the fitting model are shown in the Supplemental Table. The relevant parameters are presented in Table 1.

Table 1 KM curve optimum fitting distribution and parameters

Survival	Optimum fitting distribution	Fitting parameters			
		λ	γ	κ	η
PFS curve (penpulimab-combination group)	Weibull	0.0681 (0.0647-0.0715)	1.108 (1.053-1.164)		
PFS curve (placebo-combination group)	Log-logistic			2.790 (2.651-2.930)	4.592 (4.362-4.822)
OS curve (penpulimab-combination group)	Weibull	0.0252 (0.0239-0.0264)	1.318 (1.252-1.384)		
OS curve (placebo-combination group)	Log-logistic			1.674 (1.590-1.758)	19.474 (18.500-20.448)

Cost and utility values

Considering the Chinese healthcare system and situation of the AK105-302 clinical trial, we only evaluated the direct medical costs, including drug costs, medical management, routine follow-up, AEs, and best supportive care costs. Drug prices were obtained from public databases[15]. Medical management costs included the costs of consultations, injections, hospitalization, and nursing care, and were set at one visit per treatment cycle. After disease progression, the chemotherapy group was transitioned to receive penpulimab monotherapy. The AK105-302 trial did not provide details on post-progression medications and ratios in the experimental group under the Clinical

Guidelines for the Diagnosis and Treatment of Lung Cancer published by CSCO 2023[16], Therefore, we assumed that the experimental group would receive second-line treatment after disease progression, including best supportive care and chemotherapy (docetaxel). The costs obtained from the literature were adjusted to 2023 prices using the annual growth rate of the Chinese Consumer Price Index for Healthcare and Personal Goods. In accordance with the 2020 edition of the China Pharmacoeconomic Evaluation Guidelines[17], only AEs of grade ≥ 3 (incidence > 5%) were included, assuming that each AE occurred only once. The model inputs are shown in Table 2.

Table 2 Model inputs

Parameters	Baseline value	Ranges		Distribution	Basis of variables	Source
		Lower	Upper			
Penpulimab per 200 mg	1008.85	706.19	1311.50	Gamma	±30%	Local charge
Paclitaxel price per 175 mg/m^2	94.67	66.27	123.07	Gamma	±30%	Local charge
Carboplatin price per 5.0 mg/ml/min	30.02	21.01	39.02	Gamma	±30%	Local charge
Docetaxel price per 75mg/m^2	27.34	19.14	35.54	Gamma	±30%	Local charge
Best supportive care/cycle	336.18	235.33	437.04	Gamma	±30%	[18]
Routine follow-up cost /cycle	118.37	82.86	153.88	Gamma	±30%	[19]
Medical service costs/cycle	13.69	9.58	17.80	Gamma	±30%	[19]
Neutrophil count decreased	126.39	88.48	164.31	Gamma	±30%	[19]
Anaemia	152.48	106.74	198.23	Gamma	±30%	[19]
White blood cell decreased	126.39	88.48	164.31	Gamma	±30%	[19]
Platelet count decreased	1654.97	1158.48	2151.46	Gamma	±30%	[19]
Utility						
Utility of progression-free survival	0.856	0.813	0.899	Beta	95%CI	[20]
Utility of disease progression	0.768	0.730	0.806	Beta	95%CI	[20]
Disutility						
Neutrophil count decreased	0.20	0.14	0.26	Beta	±30%	[21]
Anaemia	0.07	0.05	0.09	Beta	±30%	[21]
White blood cell decreased	0.20	0.14	0.26	Beta	±30%	[21]
Platelet count decreased	0.11	0.08	0.14	Beta	±30%	[21]
Risk of AE						
Penpulimab plus chemotherapy group						
Neutrophil count decreased	0.45	0.32	0.59	Beta	±30%	[11]
White blood cell decreased	0.20	0.14	0.26	Beta	±30%	[11]
chemotherapy group						
Neutrophil count decreased	0.51	0.36	0.66	Beta	±30%	[11]
Anaemia	0.08	0.06	0.10	Beta	±30%	[11]
White blood cell decreased	0.21	0.15	0.27	Beta	±30%	[11]
Platelet count decreased	0.05	0.04	0.07	Beta	±30%	[11]
Others						
Discount rate	0.05	0.00	0.08	Fixed	-	[17]

Sensitivity analysis

To test the stability of each parameter on our cost-effectiveness model, one-way deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were conducted. For the one-way DSA, PFS and PD status utility values were analyzed with the 95% confidence intervals of the literature data. Other costs and AE incidence were analyzed with 30% of the basic value as the upper and lower limits, with tornado diagrams used for the output results. Second-order Monte Carlo simulations were performed for the distribution form of each parameter. The results were graphically illustrated using cost-effectiveness scatter plots and acceptability curves.

Scenario analysis

Because penpulimab had not yet been listed in the National Health Insurance Drug List (NRDL) for metastatic sq-NSCLC, we assumed that the price of penpulimab was between 0.5 times and 2 times in the NRDL.

RESULTS

Base-case analysis

The results showed a cost increase of $3,717.72 and effectiveness increase of 0.43 QALYs for the penpulimab group compared with the chemotherapy alone group, with an incremental cost-effectiveness ratio (ICER) of $8,625.78/QALY (Table 3). This was well below the WTP threshold of $38,052/QALY.

Table 3 Base-case results.

Group	Cost/$	Incremental costs	QALYs	Incremental QALYs	ICER ($/QALY)
chemotherapy	21117.32	-	1.73	-	-
penpulimab plus chemotherapy	24835.04	3717.72	2.16	0.43	8625.78

One-way DSA

The one-way PSA for the penpulimab and chemotherapy groups are presented in Figure 2. The results showed that the main parameters affecting ICER were the discount rate and penpulimab cost, with the discount rate having the greatest impact on the

results. Because the relevant parameters moved up and down within the designated range, the ICER consistently remained below the set WTP threshold, thereby corroborating the base-case analysis findings and indicating that the model was relatively stable.

PSA

The PSA scatter plot shows the incremental cost and effect data derived from 1,000 Monte Carlo simulations. As illustrated in Figure 3, the scatter plot demonstrated that the values were all below the WTP threshold in the first quadrant when WTP was set at 1× GDP per capita. Furthermore, the acceptability curves demonstrated that the penpulimab group exhibited a pronounced advantage over the chemotherapy group at WTP thresholds spanning from $12,684/QALY to $38,052/QALY (1× to 3× GDP per capita), with a 100% probability of cost-effectiveness (Figure 4).

Scenario analysis

Figure 5 shows the impact of penpulimab cost on the ICER. The cost of penpulimab varied between $252 and $1,008 (0.5 to 2 times the current price). As the cost of penpulimab increased, the ICER also increased. In all cases, the ICER was below the WTP threshold ($38,052/QALY).

DISCUSSION

In the AK105-302 clinical trial, penpulimab plus chemotherapy demonstrated significant advantages over chemotherapy alone for locally advanced or metastatic sq-NSCLC. The median PFS was prolonged by 3.4 months, with a high 30-month overall survival rate of 51.6%, and the treatment regimen was well tolerated. From this study, the NMPA approved penpulimab plus paclitaxel and carboplatin for the first-line treatment of locally advanced or metastatic sq-NSCLC. In 2021, penpulimab was approved for the treatment of relapsed or refractory classical Hodgkin's lymphoma in patients who had received at least two systemic chemotherapies[10 22]. This approval

provides Chinese NSCLC and lymphoma patients with additional therapeutic options.

As the fifth domestically produced PD-1 inhibitor, penpulimab has demonstrated promising clinical efficacy and safety. However, its cost-effectiveness has not been explored with pharmacoeconomic evidence. Here, we addressed this unmet need of a penpulimab economic evaluation. For the first time, we evaluated the cost-effectiveness of penpulimab plus chemotherapy for metastatic sq-NSCLC in China. Base-case analysis indicated that the penpulimab group displayed a greater number of QALYs, although this was accompanied by a corresponding increase in cost. When compared with the chemotherapy group, the ICER was $8,625.78/QALY, which was well below the WTP of $38,052/QALY. The sensitivity analysis indicated that the cost-effectiveness of the penpulimab group was likely to be nearly 100% at this threshold level.

In recent years, the state has actively promoted the development and application of domestically produced anticancer drugs. This initiative, coupled with a national drug price negotiation system, has resulted in a notable reduction in drug costs[23]. These measures have facilitated a gradual increase in the use of domestically manufactured anticancer drugs in the Chinese market, offering significant benefits to cancer patients in the country. Currently, penpulimab in combination with chemotherapy is not included in the National Reimbursement Database for metastatic sq-NSCLC. Therefore, we considered a broad price range for penpulimab to provide a rough assessment of the acceptability of treatment access for patients. The results showed that the ICER increased with rising penpulimab costs, which were all below the WTP threshold. Overall, the economic results indicated that this drug offers certain cost-effectiveness advantages, which are anticipated to become more pronounced after it is covered by health insurance. This study provides evidence that supports the wider use of domestically manufactured anticancer drugs.

However, this study has some limitations. Firstly, because the health utility values were not published with the results of the AK105-302 study, we choose to refer to data

from relevant Chinese NSCLC patients. This may have introduced bias into the results. Furthermore, the long-term benefits of penpulimab plus chemotherapy treatment for sq-NSCLC remain unclear. The model estimated subsequent treatment and long-term efficacy. However, the extrapolation of data from the study could have introduced bias by over- or underestimating the long-term survival outcomes. Next, we did not consider grade 1 or 2 AEs. Despite being relatively mild, these AEs can still impact the total cost. Additionally, potential changes in the clinical efficacy of penpulimab plus chemotherapy compared with chemotherapy alone for sq-NSCLC stratified by the PD-L1 tumor proportion score were not considered in this study. More detailed subgroup data will be collected in the future to explore the economic benefits. Lastly, the research perspective, modeling approach, and selection of parameter inputs may have also influenced the generalizability of our penpulimab cost-effectiveness analysis. Despite these limitations, the conclusions of our sensitivity analyses corroborated those of the base-case analysis that penpulimab plus chemotherapy represents a cost-effective treatment approach in China.

CONCLUSION

In summary, penpulimab plus chemotherapy proves to be more cost-effective than chemotherapy alone for metastatic sq-NSCLC. Furthermore, this treatment regimen is a viable and cost-effective therapeutic option within the Chinese healthcare system.

Contributors: LW, NL, CY and YG were involved in study conceptualization. LW and NL completed the data collection and analysis. LW wrote and edited the draft. XH provided the related resources and method. RD is responsible for the overall content as the guarantor. All authors approved the final manuscript.

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Figure 1 Markov models.

Figure 2 Tornado Analysis of penpulimab plus chemotherapy vs. chemotherapy.

Figure 3 The scatter plot diagram showed the probability at the current WTP threshold.

Figure 4 Cost-effectiveness acceptability curves for penpulimab plus chemotherapy vs.

chemotherapy.

Figure 5. Results of scenario analysis.

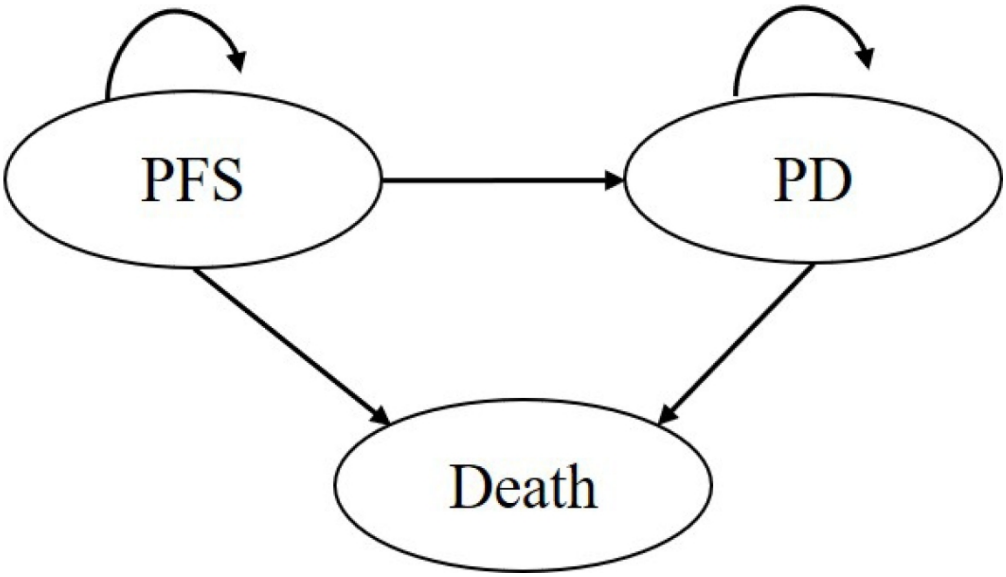

Figure 1 Markov models.

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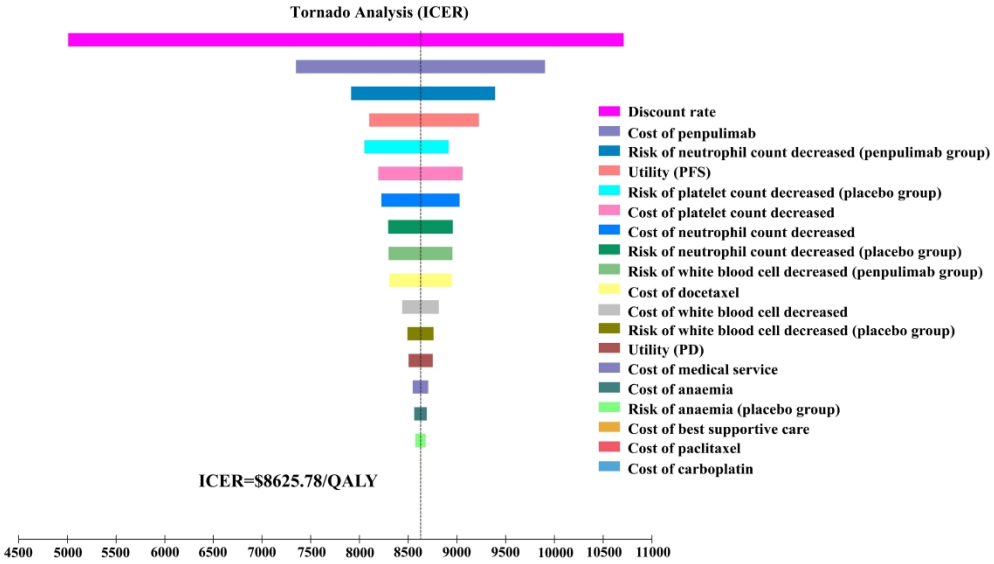

Figure 2 Tornado Analysis of penpulimab plus chemotherapy vs. chemotherapy.

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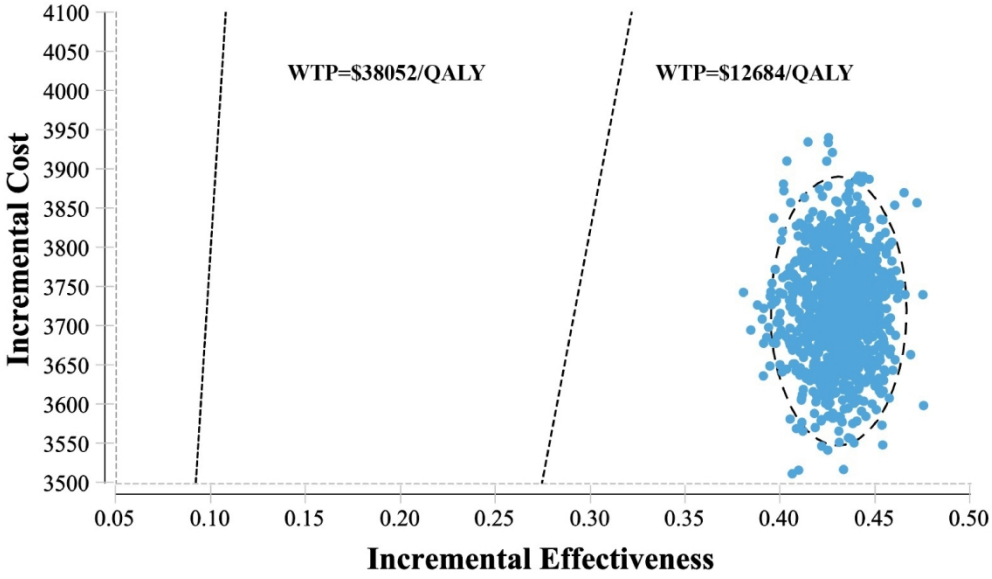

Figure 3 The scatter plot diagram showed the probability at the current WTP threshold.

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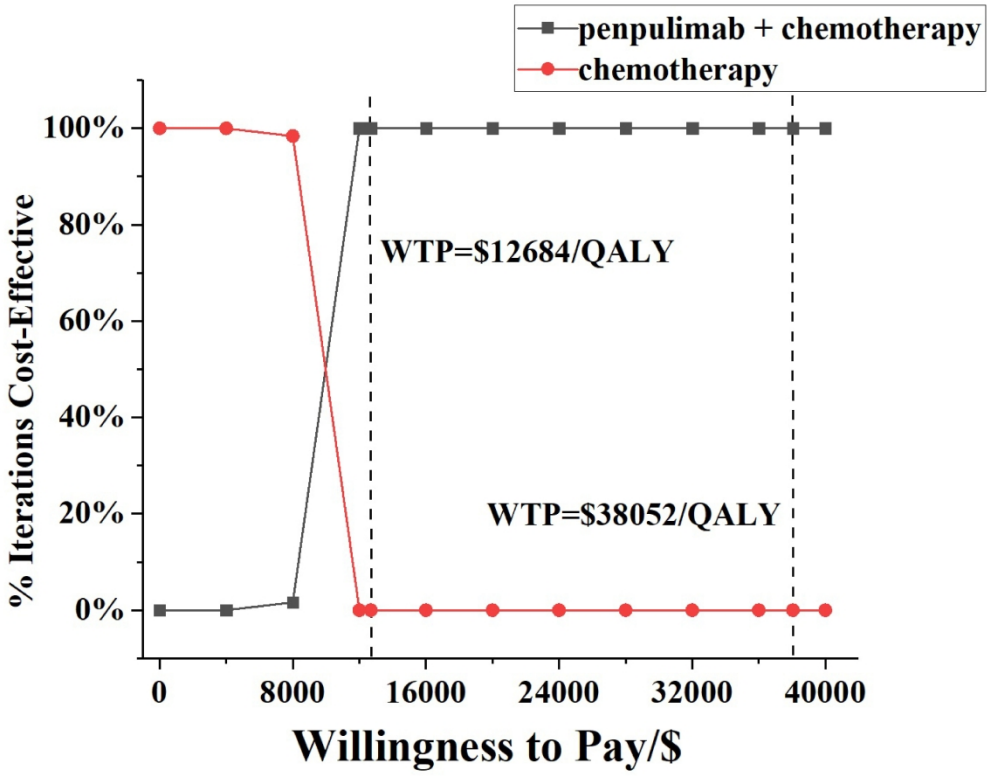

Figure 4 Cost-effectiveness acceptability curves for penpulimab plus chemotherapy vs. chemotherapy.

187x146mm (800 x 800 DPI)

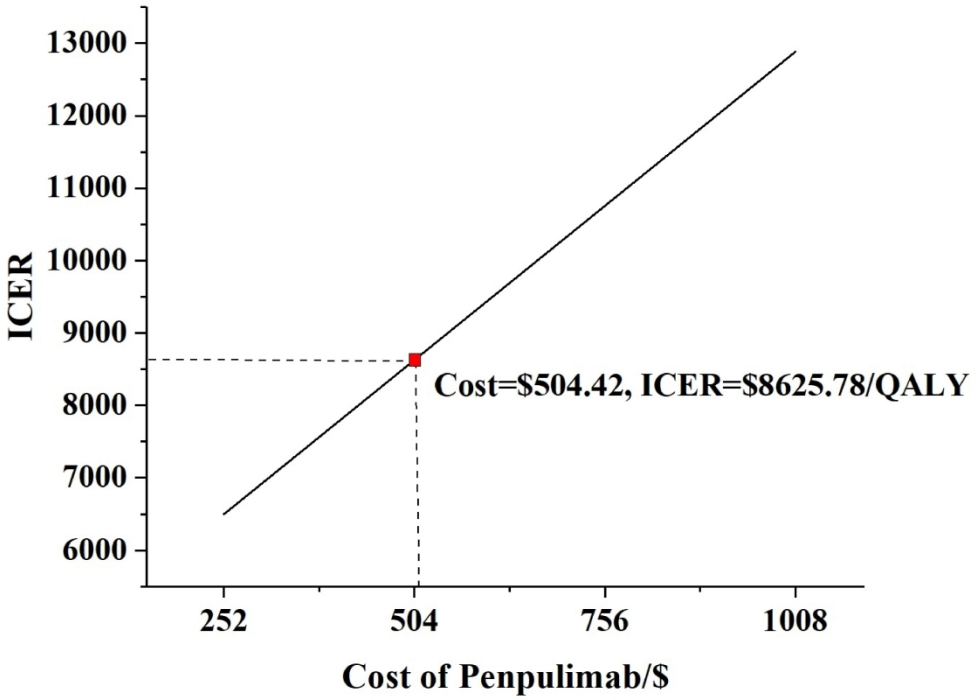

Figure 5. Results of scenario analysis.

186x143mm (600 x 600 DPI)

Table

AIC and BIC values of different K-M curve fitting distributions

	Group	Survival curve	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
AIC	penpulimab+chemotherapy	PFS	844.2596	844.4775	844.3246	820.5727	823.8946
		OS	665.0947	661.4978	663.1322	663.6693	661.7181
	placebo+ chemotherapy	PFS	836.3011	816.5411	838.3007	764.1781	745.8202
		OS	840.7221	831.6527	836.2086	837.0231	831.0435
BIC	penpulimab+chemotherapy	PFS	847.4244	850.8071	850.6542	826.9022	830.2242
		OS	668.2595	667.8274	669.4618	669.9988	668.0477
	placebo+ chemotherapy	PFS	839.4659	822.8707	844.6303	770.5077	752.1498
		OS	843.8869	837.9823	842.5382	843.3527	837.3731