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Original Article

Cost-effectiveness analysis of trilaciclib for preventing myelosuppression in small cell lung cancer patients treated with etoposide, carboplatin, and atezolizumab

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Abstract: This study evaluated the economic value of administering trilaciclib to prevent myelosuppression in extensive-stage small cell lung cancer (ES-SCLC) patients receiving etoposide, carboplatin, and atezolizumab (E/P/A) from both the Chinese and the United States (US) perspectives. A decision tree model was constructed to estimate and compare costs, quality-adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs), incremental net health benefits (INHBs), and incremental net monetary benefits (INMBs). One-way and probabilistic sensitivity analyses were conducted to assess the robustness and uncertainty of the economic analysis. The base case analysis indicated that from the perspective of US payers, trilaciclib was cost-saving at the WTP threshold of $241,230.00, with an incremental cost of $-12,626.08, an INMB of $16,788.02, and an INHB of 0.07 QALYs. Conversely, from the perspective of Chinese payers, the use of trilaciclib was not economical at the WTP threshold of $35,817.44, with an ICER of $691,541.63/QALY, an INMB of -$8,765.52, and an INHB of -0.24 QALYs. Sensitivity analysis confirmed the stability of these results. Probabilistic sensitivity analysis indicated that, from the Chinese payers' perspective, trilaciclib treatment was not economical, with a probability of 100%. In contrast, from the US payers' perspective, it was economical, with a probability of 90.05%. Given the limited clinical data available for trilaciclib in the Chinese population, the cost-effectiveness of trilaciclib may improve with the inclusion of new data or changes in health insurance policies.

Keywords: Trilaciclib, cost-effectiveness, small cell lung cancer, myelosuppression, atezolizumab

Introduction

Lung cancer is one of the most prevalent cancers and has the highest mortality rate in both men and women [1]. Small cell lung cancer (SCLC) is a type of neuroendocrine tumor that accounts for approximately 15% of lung cancers and is highly aggressive, poorly differentiated, and highly malignant [2]. SCLC can be classified into two categories: limited-stage SCLC and extensive-stage SCLC (ES-SCLC) [3]. Approximately 60-70% of SCLC patients are already in the extensive stage at the time of diagnosis. The prognosis of SCLC patients is very poor, with a median survival of 8-12 months and a 5-year survival rate of less than 7% [4, 5].

Platinum plus etoposide has been a common therapeutic regimen for SCLC for the past few decades, and the current National Comprehensive Cancer Network (NCCN) guidelines recommend a regimen of 4-6 cycles for treating ES-SCLC [6]. Recent studies have shown that the addition of immune checkpoint inhibitors (ICIs) to chemotherapy regimens can improve outcomes, leading to guidelines suggesting their use as first-line treatments [7, 8]. Atezolizumab, an approved ICI, is used in combination with chemotherapy for the treatment of ES-SCLC patients in countries such as the United States (US) and China [9]. Several studies have reported that atezolizumab plus chemotherapy can improve overall survival (OS) and progression-free survival in ES-SCLC patients compared with chemotherapy alone [10, 11]. Despite the demonstrated efficacy, the adverse reactions (ADRs) associated with antitumor therapy still cannot be ignored.

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Myelosuppression, manifesting as leukocytopenia, neutropenia, anemia, or thrombocytopenia, remains a major adverse reaction to chemotherapy combined with immunotherapy. Severe cases can progress to febrile neutropenia (FN). As defined by the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, severe myelosuppression (Grade ≥ 3) involves a hemoglobin concentration less than 80 g/L, a white blood cell count less than 2×10^9/L, a neutrophil count less than 1×10^9/L or a platelet count 50×10^9/L [12]. Approximately 60% of patients experience grade 3 or greater myelosuppression adverse events (AEs), predominantly neutropenia, anemia, or thrombocytopenia [13]. Severe myelosuppression can lead to dose reductions, treatment delays, increased hospitalization rates and longer hospital stays and impose a significant burden on ES-SCLC patients [14].

Trilaciclib, a cyclin-dependent kinase 4/6 inhibitor, was approved by the Food and Drug Administration (FDA) and National Medical Products Administration (NMPA) in 2021 and 2022, respectively, to reduce the incidence of chemotherapy-induced myelosuppression in ES-SCLC patients [15, 16]. Clinical studies have shown that trilaciclib can reduce myelosuppression and improve health-related quality of life and safety profiles in ES-SCLC patients receiving carboplatin, etoposide and atezolizumab (E/P/A) [17]. However, importantly, the cost of immunotherapy and chemotherapy is already higher than that of chemotherapy alone, and administering trilaciclib further increases treatment costs, given its high price in both the US and China. Despite its clinical efficacy, the economic value of trilaciclib must also be considered.

This study aims to compare the cost-effectiveness of using trilaciclib versus not using trilaciclib in ES-SCLC patients receiving E/P/A from the perspectives of both US and Chinese payers.

Methods

Model overview

The design and execution of this cost-effective analysis were guided by the consolidated health economic evaluation reporting standards (CHEERS) reporting guidelines [18]. Currently, decision tree and Markov models are widely used in economic evaluations. Decision tree models offer static, short-term simulations suitable for estimating the total costs and health outcomes of interventions within brief treatment periods. In contrast, Markov models are better suited for evaluating chronic conditions that evolve over time. Given that guidelines recommend 4 to 6 cycles of chemotherapy or chemotherapy combined with ICIs for ES-SCLC, we opted for a decision tree model to assess the cost-effectiveness of trilaciclib in preventing myelosuppression during this treatment period. TreeAge software (vision 2022) was used to construct a decision tree model and assess the cost-effectiveness of trilaciclib versus no trilaciclib in patients with ES-SCLC from the perspective of the US and Chinese payers. The outcomes measured included costs, quality-adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs), incremental net health benefits (INHBs) and incremental net monetary benefits (INMBs). The study included ES-SCLC patients (≥ 18 years old) receiving initial treatment. The patient characteristics assumed were as follows: age 61 years, body weight 65 kg, total body surface area 1.80 m^2, creatinine clearance 90 mL/min/1.73 m^2, and an area under the curve (AUC) of 5 mg/mL/min [19, 20].

The decision tree model depicted in **Figure 1** offers two treatment options for ES-SCLC patients: E/P/A plus trilaciclib or E/P/A plus placebo. The therapeutic schedule comprises induction and maintenance phases. During induction, patients received atezolizumab (1200 mg, day 1), carboplatin (AUC = 5 mg/mL/min, day 1), and etoposide (100 mg/m^2, days 1-3) per cycle, with trilaciclib (240 mg/m^2) or placebo administered before each cycle for 3 days. The maintenance treatment involved atezolizumab monotherapy on day 1 of each cycle. According to the NCCN guidelines, a chemotherapy cycle lasts 21 days, with a minimum of four cycles and a maximum of six cycles [21]. The decision tree model's time horizon was set at four chemotherapy cycles (12 weeks). In this model, patients were categorized into two AE conditions: hematological AEs and nonhematological AEs. Other AEs (e.g., nausea, vomiting, drowsiness) were grouped under nonhematological AEs. Only ≥ grade 3 AEs were included in the economic analysis, as lower-grade events

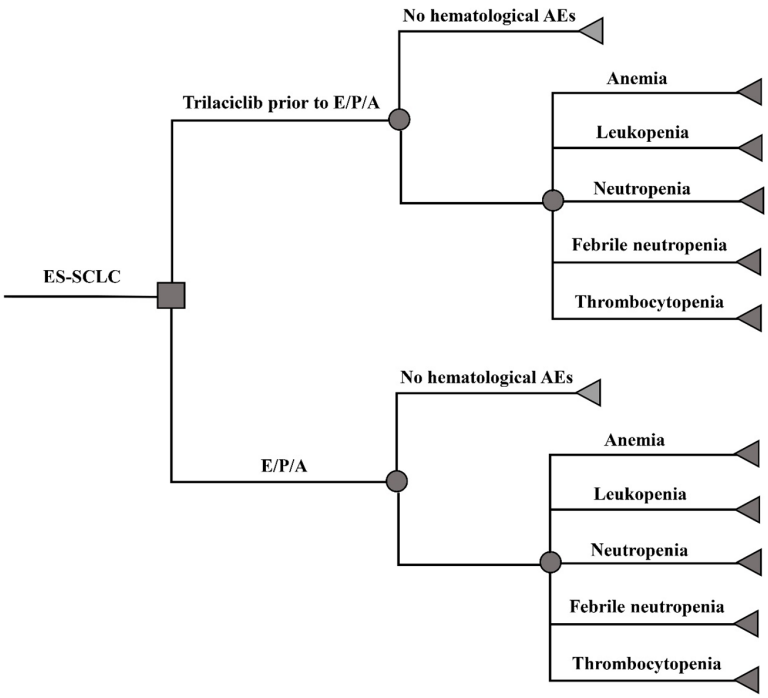

Figure 1. Decision tree model structure. Abbreviations: AE, adverse event; E/P/A, etoposide, carboplatin and atezolizumab; ES-SCLC, extensive-stage small cell lung cancer.

were assumed to have minimal impact on outcomes. The per capita gross domestic product (GDP) was $11,939.15 in China and $80,410.00 in the US [22, 23]. Following World Health Organization guidelines, the willingness-to-pay (WTP) threshold was set at three times the GDP, resulting in $35,817.44/QALY gained for China and $241230.00/QALY for the US [24].

Costs

The data for the economic analysis were sourced from official websites and the relevant literature. We conducted a literature search using terms such as 'trilaciclib', 'small cell lung cancer', 'cost-effectiveness', and 'economics' in the PubMed and Cochrane Library databases. Clinical studies and economic evaluations focused on the prevention of myelosuppression in SCLC patients receiving chemotherapy combined with ICIs using trilaciclib, as well as economic analyses related to SCLC chemotherapy or ICI treatments, were included. We excluded duplicate studies, those presenting subgroup or pooled analyses from the same clinical trial, and studies with incomplete information. For multiple similar studies, the most recent findings were selected for this analysis.

All the parameters included in this model are listed in **Table 1**. In this economic analysis, only direct medical costs were included, and non-medical direct costs were excluded. The direct medical costs in this model encompassed drug costs, AE management costs, prophylactic granulocyte colony-stimulating factor (G-CSF) use costs, and follow-up costs, such as administration, laboratory, tumor imaging, and best supportive care costs. All costs were converted into US dollars at the exchange rate noted for October 2023 (1 USD = 7.1782 RMB) [25]. Given that the time horizon for this analysis was less than one year, discounting was not applied. The drug prices in China were obtained from the Yaozhi database for 2023 [26], and those in the US were obtained from the Centers for Medicare & Medicaid Services [27]. The cost of using G-CSF to prevent myelosuppression was reported in a previous study [28]. Severe AEs (grade ≥ 3), including decreased white blood cell count, neutropenia, FN, anemia, and thrombocytopenia, were considered in this analysis. The AE management costs in China were derived from two studies conducted in 2021 and 2023 [29, 30], whereas those in the US were obtained from two other studies [28, 31]. Costs for administration, laboratory tests, tumor imaging, and best supportive care in China were sourced from a study conducted in 2022 [20], whereas these costs in the US were extracted from the study of Shao T et al. [31]. Tom's inflation calculator was used for cost adjustments [32]. All costs in this study have been uniformly adjusted to 2023 values.

Outcome measures

The health utility values for patients in the trilaciclib and placebo groups were extracted from the study of Abraham I et al. [33]. Disutilities due to myelosuppression-related

Table 1. Parameters and ranges in the decision tree model

Parameter	China Value	US Value	Distribution
Drug cost, $			
Trilaciclib	833.11 (666.49-999.73)[a] [26]	5.20 (4.16-6.24)[e] [27]	Gamma
Etoposide	12.54 (10.03-15.05)[b] [26]	0.77 (0.61-0.92)[f] [27]	
Carboplatin	19.79 (15.83-23.75)[c] [26]	2.76 (2.21-3.31)[g] [27]	Gamma
Atezolizumab	4,569.58 (3,655.67-5,483.50)[d] [26]	82.62 (66.10-99.15)[h] [27]	
G-CSFs, per cycle	111.11 (88.89-133.33) [26]	6,383.58 (5,106.86-7,660.30) [27, 28]	Gamma
Cost of managing AEs ($)			
Anemia	550.15 (440.12-660.18) [30]	27,690.02 (22,152.02-33,228.02) [31]	Gamma
White blood cell count decreased	504.47 (403.59-605.36) [30]	13,511.26 (10,809.01-16,213.51) [31]	Gamma
Neutropenia	91.16 (72.93-109.39) [30]	23,482.18 (18,785.74-28,178.62) [31]	Gamma
Febrile neutropenia	4,109.15 (3,287.32-4,930.98) [29]	25,123.45 (20,098.76-30,148.14) [28]	Gamma
Thrombocytopenia	1,141.01 (912.81-1,369.21) [30]	31,021.55 (24,817.24-37,225.86) [31]	Gamma
Other costs ($)			
Administration per cycle	37.12 (29.70-44.54) [20]	162.02 (129.62-194.42) [31]	Gamma
Laboratory per cycle	171.15 (136.92-205.38) [20]	116.27 (93.02-139.52) [31]	Gamma
Tumor imaging per cycle	522.72 (418.18-627.26) [20]	451.79 (361.43-542.15) [31]	Gamma
Best supportive care per cycle	227.85 (182.28-273.42) [20]	1,492.67 (1,194.14-1,791.20) [31]	Gamma
Risk of AEs in the trilaciclib group			
Hematological AEs	0.2440 (0.1952-0.2928) [36]	0.3654 (0.3289-0.4019) [17]	Beta
Anemia	0.2400 (0.2160-0.2640) [36]	0.2223 (0.2001-0.2445) [35]	Beta
White blood cell count decreased	0.0800 (0.0720-0.0880) [36, 37]	0.0556 (0.0500-0.0612) [35]	Beta
Neutropenia	0.1600 (0.1440-0.1760) [36]	0.4333 (0.3900-0.4766) [35]	Beta
Febrile neutropenia	0.0400 (0.0360-0.0440) [36]	0.0444 (0.0400-0.0488) [35]	Beta
Thrombocytopenia	0.4800 (0.4320-0.5280) [36]	0.2444 (0.2200-0.2688) [35]	Beta
Risk of AEs in the placebo group			
Hematological AEs	0.4520 (0.3616-0.5242) [36]	0.7358 (0.6622-0.8094) [17]	Beta
Anemia	0.1860 (0.1671-0.2043) [36]	0.2094 (0.1885-0.2303) [35]	Beta
Decreased white blood cell count	0.2570 (0.2314-0.2829) [36, 37]	0.1047 (0.0942-0.1152) [35]	Beta
Neutropenia	0.2860 (0.2571-0.3143) [36]	0.4241 (0.3817-0.4665) [35]	Beta
Febrile neutropenia	0.1000 (0.0900-0.1100) [36]	0.0576 (0.0518-0.0634) [35]	Beta
Thrombocytopenia	0.1710 (0.1543-0.1886) [36]	0.2042 (0.1838-0.2246) [35]	Beta
Other			
Prophylactic use of G-CSF in the trilaciclib group	0.3230 (0.2907-0.3553) [36]	0.2963 (0.2667-0.3259) [17]	Beta
Prophylactic use of G-CSF in the placebo group	0.5030 (0.4527-0.5533) [36]	0.4717 (0.4245-0.5189) [17]	Beta
Utility			
Trilaciclib group	0.650 (0.455-0.845) [33]		Beta
Placebo group	0.630 (0.441-0.819) [33]		Beta
Disutility			
Anemia	0.070 (0.050-0.090) [31]		Beta
Decreased white blood cell count	0.200 (0.140-0.260) [31]		Beta
Neutropenia	0.090 (0.060-0.120) [31]		Beta
Febrile neutropenia	0.470 (0.330-0.610) [34]		Beta
Thrombocytopenia	0.200 (0.140-0.260) [20]		Beta
Other			
Average number of chemotherapy cycles	4 (4-6) [6]		
Average number of prophylactic G-CSF cycles	3.41 (0-6) [33]		
Body surface area (meters^2)	1.80 (1.44-2.16) [19]		Normal
Area under the curve (mg/mL/min)	5 [20]		Fixed
Creatinine clearance rate, mL/min/1.73 m^2	90 (80-100) [19]		Normal

a: The cost of 300 mg trilaciclib; b: The cost of 100 mg etoposide; c: The cost of 100 mg carboplatin; d: The cost of 1200 mg atezolizumab; e: The cost of 1 mg trilaciclib; f: The cost of 10 mg etoposide; g: The cost of 50 mg carboplatin; h: The cost of 10 mg atezolizumab. Abbreviations: AEs, adverse events; G-CSF, granulocyte colony-stimulating factor.

AEs were obtained from three other studies [20, 31, 34]. The OS data of ES-SCLC patients in the US, with and without trilaciclib, were based on a pooled study [35], whereas the OS

data for Chinese patients were derived from one clinical study [36]. The quality-adjusted life years (QALYs) for each treatment were estimated by multiplying the utility weights by the life years, which were calculated as the time horizon (12 weeks) divided by 52 weeks.

The total hematological AE rates in US patients were derived from the RCT by Daniel et al. [17], whereas the proportions of various hematological AEs were obtained from a pooled study [35]. The RCT reported in 2024 [36] did not report hematological AE rates for Chinese patients; thus, we assumed that the incidence of ≥ grade 3 hematological AEs aligns with the chemotherapy dose reduction rate. Since the incidence of ≥ grade 3 white blood cell count was not reported in this RCT, we calculated it indirectly. A pooled analysis of anemia, neutropenia, febrile neutropenia, and thrombocytopenia yielded a risk ratio of 0.42 [0.17-1.01] for hematological AEs in the E/P/A + trilaciclib group compared with the E/P/A group. This RR was then multiplied by the incidence of decreased white blood cell count from another study in the Chinese population [37] to determine the incidence in the E/P/A + trilaciclib group.

Base case analysis

In this economic analysis, outcomes, including incremental cost, incremental QALYs, the ICER, INHB and INMB, were evaluated. The incremental cost and incremental QALYs were calculated by the cost or QALYs in the trilaciclib group minus those in the placebo group. The ICER was calculated by dividing the incremental costs by the incremental QALYs. The INMB and INHB, which are also important parameters of cost-effectiveness analysis, were evaluated using the following formulas: INMB = $\Delta E \times WTP - \Delta C$, INHB = $\Delta E - \Delta C/WTP$. Here, ΔE represents incremental QALYs, and ΔC represents incremental costs [38, 39]. An ICER > WTP, an INMB < 0, or an INHB < 0 indicates that the treatment is not economical; otherwise, the treatment is considered economical.

Sensitivity analyses

Given that this study relied on several assumptions and that most of the data were derived from the literature, one-way and probabilistic sensitivity analyses were conducted to evaluate the robustness and uncertainty of the base case results. In the one-way sensitivity analyses, the total probability of hematological AEs and the cost due to AEs were varied by ±20% of the baseline value, utility variables and disutility due to AEs were varied by ±30%, and the probability of each type of hematological AE was varied by ±10%. A tornado diagram was used to present the results of the one-way sensitivity analysis. Variables that may impact ICER values, as identified in the tornado diagram, were further analyzed by expanding their ranges in a separate one-way sensitivity analysis to determine the thresholds affecting the cost-effectiveness analysis results.

Additionally, since simultaneous variations in multiple variables could influence the model outcomes, a probabilistic sensitivity analysis using 10,000 Monte Carlo simulations was performed. In this analysis, cost variables were assumed to follow a gamma distribution, the creatinine clearance rate and body surface area were assumed to follow a normal distribution, and the utility and probability variables were assumed to follow a beta distribution. However, the area under the curve (AUC), average number of prophylactic G-CSF cycles and number of chemotherapy cycles were not standardized. Cost-effectiveness acceptability curves comparing trilaciclib and placebo prior to E/P/A were generated to analyze the economics of the two regimens across varying WTP thresholds. Scatterplots of the ICERs were created to illustrate the distributions of incremental costs and incremental QALYs when multiple variables changed simultaneously.

Results

Base case results

The total cost, incremental cost, ICERs, INMB, and INHB for each regimen are summarized in **Table 2**. In China, compared with the placebo, the use of trilaciclib increased costs by $9,244.32, increased QALYs by 0.01, and resulted in an ICER of $691,541.63/QALY. Additionally, at the WTP threshold of 35,817.44/QALY, the INMB and INHB of trilaciclib before E/P/A were $-8,765.52 and -0.24 QALYs, respectively. In the US, trilaciclib administered before E/P/A was associated with a cost savings of $12,626.08 per patient and a gain of 0.02 QALYs. The INMB and INHB of trilaciclib

Table 2. Cost-effectiveness analysis results

Parameter	China		United States	
	E/P/A group	E/P/A + trilaciclib group	E/P/A group	E/P/A + trilaciclib group
WTP value, $/QALY	35,817.44		241,230.00	
Total cost $	24,592.54	33,836.87	132,552.77	119,926.68
QALYs	0.13	0.14	0.12	0.14
Incremental cost $	NA	9,244.32	NA	-12,626.08
Incremental QALYs	NA	0.01	NA	0.02
ICER $/QALY	NA	691,541.63	NA	NA
INMB, $	NA	-8,765.52	NA	16,788.02
INHB, QALY	NA	-0.24	NA	0.07

Abbreviations: E/P/A, etoposide, carboplatin, and atezolizumab; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefits; INMB, incremental net monetary benefits; QALY, quality-adjusted life year; WTP, willingness-to-pay.

given before E/P/A were $16,788.02 and 0.07 QALYs, respectively, at the WTP thresholds of $241,230.00/QALY. This base case analysis demonstrated that administering trilaciclib before the E/P/A was the most economical strategy in the US, whereas the opposite was true in China.

One-way sensitivity analyses

The results of the one-way sensitivity analysis are presented in the tornado diagram in **Figure 2**. According to the presented tornado diagrams, 39 parameters related to ICERs were analyzed for both China and the US. The tornado diagram revealed that the three most important variables were the probability of hematological AEs in the placebo group, the average number of chemotherapy cycles, and the cost of trilaciclib in China (**Figure 2A**), whereas the two most important variables in the US were the probability of hematological AEs in the trilaciclib group and the placebo group (**Figure 2B**). However, regardless of which parameter varies independently within the given range, trilaciclib remains economical for American patients and uneconomical for Chinese patients, which is consistent with the baseline analysis. Furthermore, expanding the scope of one-way sensitivity analysis revealed that only when the cost of trilaciclib was below $102.65/300 mg was the ICER value lower than the WTP threshold; that is, treatment with trilaciclib was considered economical from the perspective of Chinese payers (Figure S1). Even with an expanded probability of hematological AEs in the placebo group (Figure S2) and an average number of chemotherapy cycles (Figure S3), trilaciclib is not economical in Chinese patients. However, from the perspective of US payers, when the probability of hematological AEs in the placebo group was lower than 0.58 (Figure S4) or when the probability of hematological AEs in the trilaciclib group was higher than 0.52 (Figure S5), trilaciclib no longer represented a cost-saving strategy.

Probabilistic sensitivity analyses

Scatter plots are shown in **Figure 3**. All of the ICERs were greater than the WTP threshold from the perspective of Chinese payers (**Figure 3A**); that is, trilaciclib administered before E/P/A was unlikely to be cost effective. However, **Figure 3B** demonstrates that when multiple factors varied simultaneously within a certain range, 90.05% of the ICERs were lower than the WTP threshold, indicating that treatment with trilaciclib prior to E/P/A was more economical than treatment with E/P/A from the perspective of US payers. The cost-effectiveness acceptability curves of the different treatments are shown in **Figure 4**. In China, trilaciclib administered before E/P/A was more cost-effective only when the WTP thresholds increased over 22-fold ($187,983.68) (**Figure 4A**). However, in the US, regardless of the variation in the WTP threshold across a 20-fold range, administering trilaciclib before E/P/A remains more economical, with a probability exceeding 70% (**Figure 4B**).

Discussion

Treatment with platinum plus etoposide chemotherapy with or without ICIs is recommended as the standard first-line treatment. A previ-

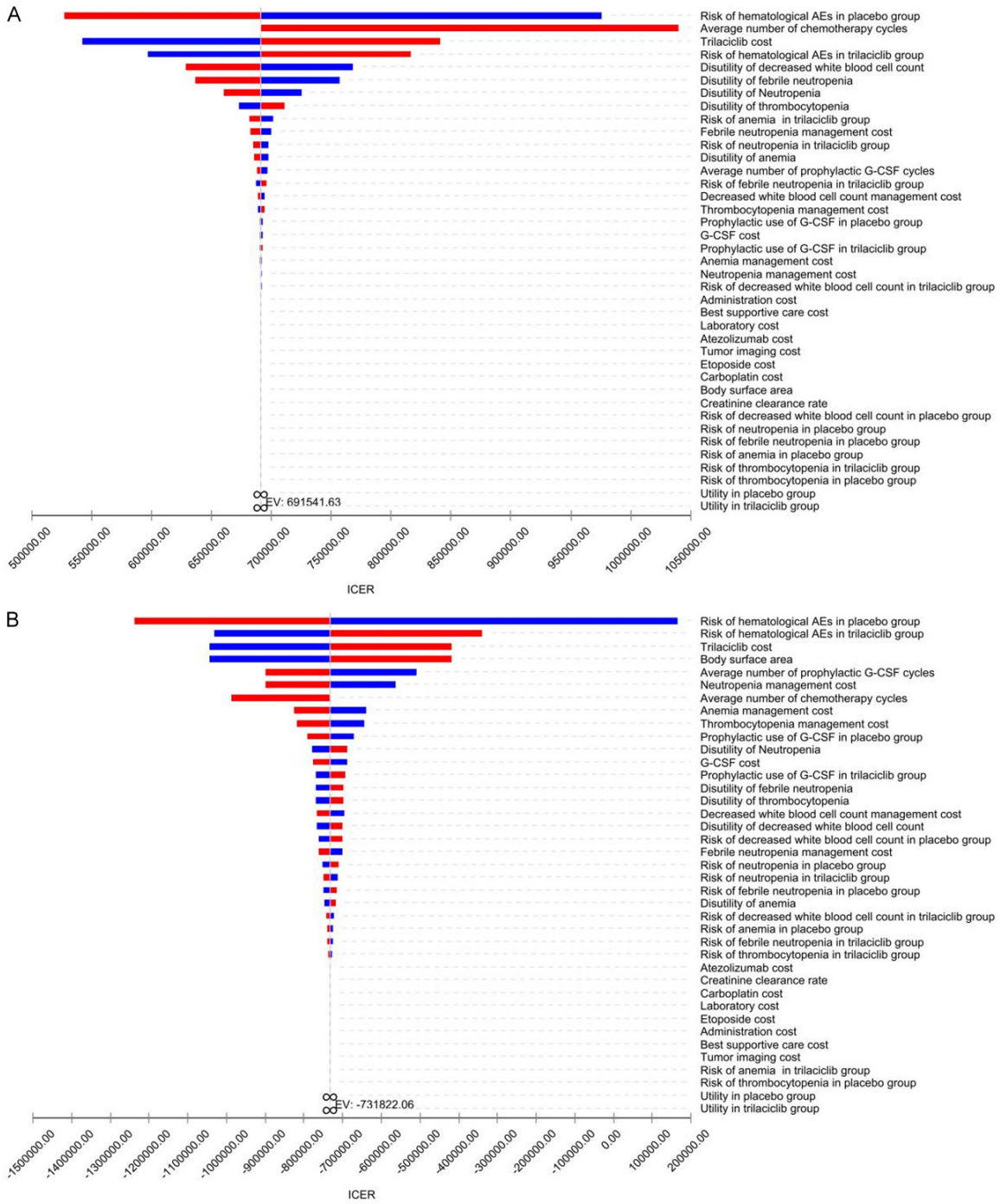

Figure 2. Tornado diagram of one-way sensitivity analyses. A. One-way deterministic sensitivity analysis results for base cases from the Chinese payer perspective. B. One-way deterministic sensitivity analysis results for base cases from the US payer perspective. Abbreviations: AE, adverse event; G-CSF, granulocyte colony-stimulating factor.

ous Bayesian network meta-analysis revealed that ICIs combined with chemotherapy are often associated with ≥ 3 grade hematological AEs, including neutropenia, leukopenia, thrombocytopenia, and anemia [40]. Trilaciclib, a newly approved drug for preventing chemotherapy-induced myelosuppression, has not yet been evaluated economically in China. This study is the first to assess the economic value of trilaciclib in preventing myelosuppression in

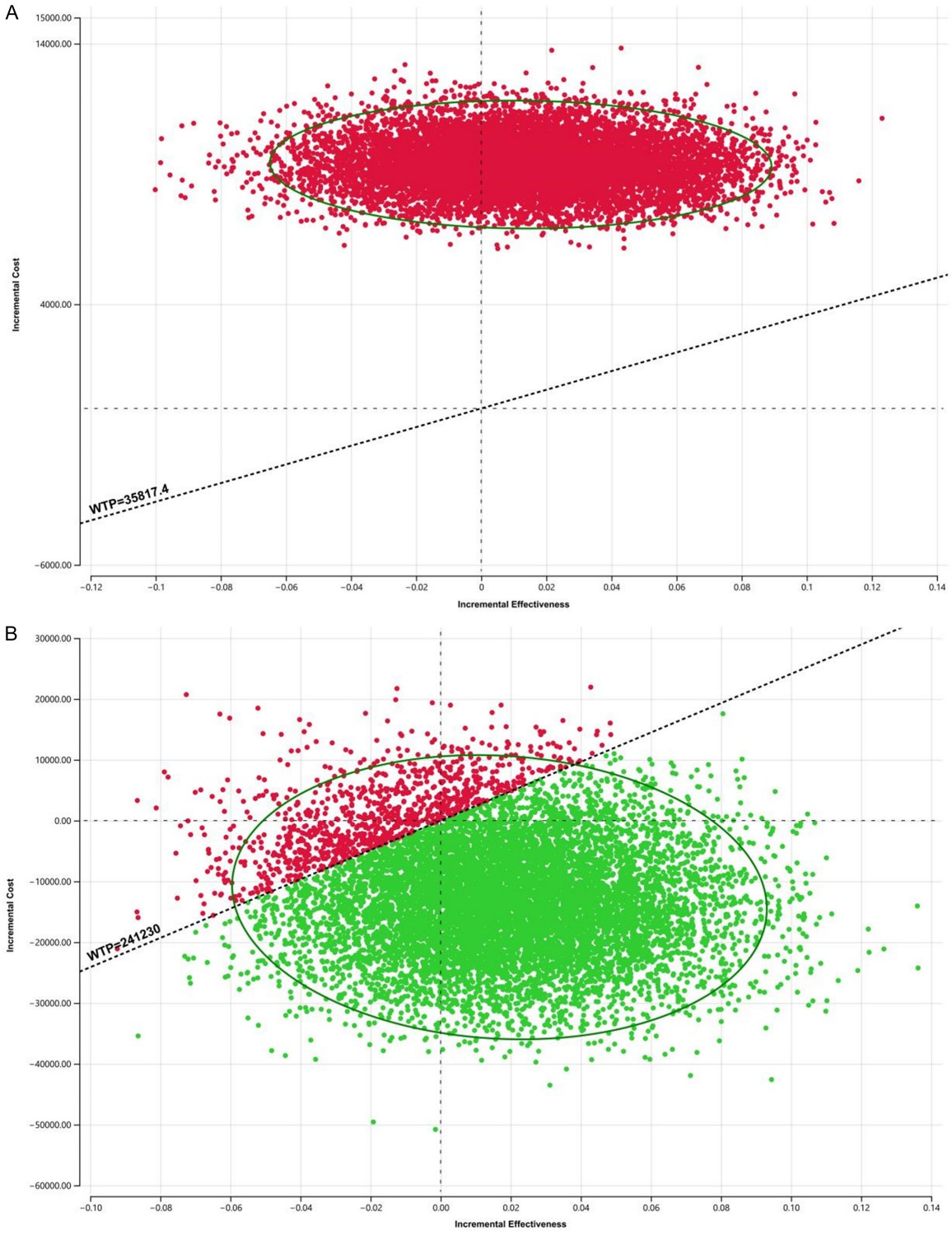

Figure 3. Scatter plot of the incremental cost and effectiveness of E/P/A + trilaciclib compared with E/P/A alone. A. Scatter plot from the Chinese payer perspective. B. Scatter plot from the US payer perspective.

a Chinese population and to compare its economic value from the perspectives of both US and Chinese payers.

From the Chinese payer perspective, the base case analysis estimated that the ICER for trilaciclib administered before E/P/A was higher

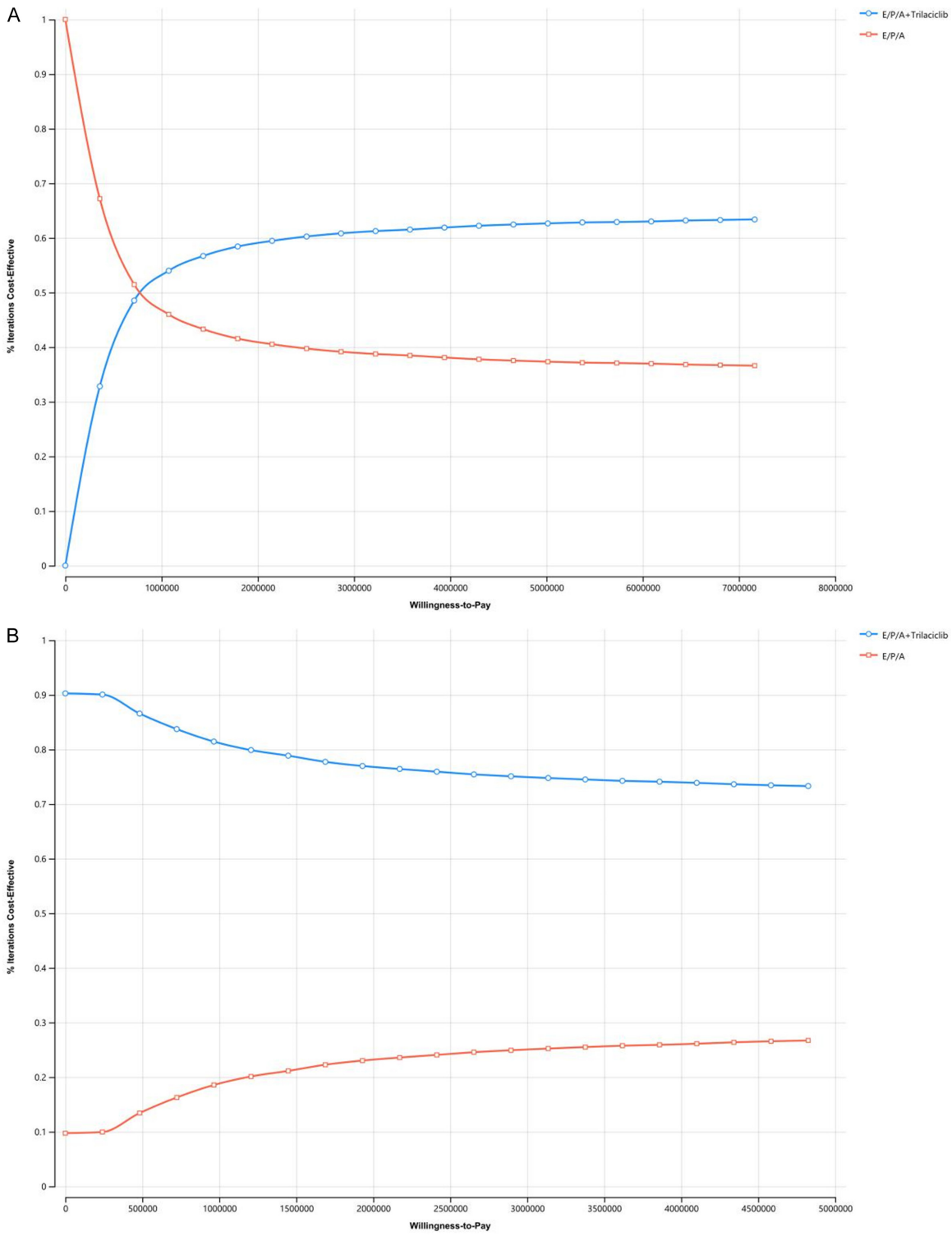

Figure 4. Cost-effectiveness acceptability curves. A. Cost-effectiveness acceptability curve from the Chinese payer perspective. B. Scatter plot from the US payer perspective.

than the WTP threshold. Probabilistic sensitivity analysis further indicated a low probability of cost-effectiveness at this threshold. Conversely, the economic analysis for the US shows the opposite result. Additionally, INMB and INHB were also used for economic evaluation [41].

Our study revealed that both are negative in the Chinese patient population but positive in the U.S. patient population. Overall, trilaciclib is not economical for preventing myelosuppression in China but is more economical in the US. This finding is consistent with a previous US economic analysis [33]. Many factors may have contributed to these outcomes, such as the cost of chemotherapy and immunotherapy, trilaciclib pricing, hematological AE management costs, and the risk of hematological AEs.

One-way sensitivity analysis allows us to explore the impact of varying one parameter at a time on the outcomes of our economic evaluation. This helps us identify which parameters have the most significant influence on the results and understand the key drivers of the cost-effectiveness analysis. The most likely factors identified by our one-way sensitivity analysis differ from those identified in previous studies [33], possibly due to the different parameters used in the respective study models. The tornado diagram shows that the price of trilaciclib is an important factor. The economic analysis revealed that its cost-effectiveness in China is sensitive to its price. One-way sensitivity analysis confirmed that reducing the drug price could improve economic outcomes. Specifically, trilaciclib becomes cost-effective at WTP thresholds if its price is lower than $102.65/300 mg. However, this threshold is based on current research, and the price may change as more clinical study results from Chinese patients are reported. Nonetheless, evolving national healthcare policies in China are likely to reduce costs and benefit more patients. Moreover, chemotherapy and ICIs are costly for both Chinese and American patients. Two economic studies have indicated that atezolizumab combined with chemotherapy is not cost-effective for ES-SCLC patients from an American perspective [42, 43]. A Chinese study reported similar findings, showing that atezolizumab plus chemotherapy is not more economical than chemotherapy alone [44]. Adding the more expensive trilaciclib to atezolizumab and chemotherapy is therefore expected to be less cost-effective. Our analysis confirms that this regimen is uneconomical in China. However, our study revealed that trilaciclib is cost effective in the US. This discrepancy may be due to several factors. Trilaciclib, a new drug for preventing myelosuppression, faces varying pricing influences in both China and the US, including market demand, tax burdens, patent protection, and health insurance policies. Patent protection and taxes contribute to higher prices when the drug enters the Chinese market compared to the original country. Although the Chinese government has been using centralized procurement and price negotiations to lower drug prices and improve accessibility, trilaciclib has not yet been included in these programs, keeping its price relatively high. Moreover, China's health insurance system, which is primarily public, includes schemes such as urban employee basic medical insurance and urban resident basic medical insurance, which cover a large portion of the population but may have limited coverage for expensive, innovative drugs such as trilaciclib. In contrast, the US health insurance system may offer broader coverage for drug expenses, thereby indirectly lowering the market price for patients.

In addition, according to the two tornado diagrams obtained in our study, the probabilities of hematological AEs in both the trilaciclib group and the placebo group are important influencing factors for the results of the cost-effectiveness analysis. Further one-way sensitivity analysis revealed that, for Chinese patients, regardless of how the total probability of hematological AEs varies between 0 and 1 in either the trilaciclib group or the placebo group, the cost-effectiveness analysis remains robust, indicating that the use of trilaciclib for the prevention of myelosuppression is not economical. For American patients, however, if the total probability of hematological AEs in the placebo group lower than 0.58, the cost-effectiveness analysis outcome reverses. Similarly, if the probability in the trilaciclib group higher than 0.52, the cost-effectiveness analysis outcome also reversed, suggesting that trilaciclib is not cost-effective. These findings from the one-way sensitivity analysis indicate that more clinical studies are needed to further validate the results of the cost-effectiveness evaluation of trilaciclib in the US. It is possible that the results of this study might also change when performed with updated data from the US patient population.

The probabilistic sensitivity analysis addresses overall uncertainty in the economic evaluation by considering the joint uncertainty of multiple

input variables. By assigning distributions to each input parameter and conducting Monte Carlo simulations, we obtained a range of possible outcomes and probabilities associated with different cost-effectiveness thresholds. Although the aforementioned factors may influence the results of the base case cost-effectiveness analysis, the probabilistic sensitivity analysis indicates that our base case findings are stable and reliable. Furthermore, the results of our probabilistic sensitivity analysis are similar to those of a previous study [33].

Several limitations should be considered in this study. First, this study was conducted from the perspective of payers and did not include indirect medical costs. Thus, the costs in this study may be underestimated. From other perspectives, the results may be different. Second, in this study, our analysis is based on several key assumptions. We assumed that the utility values of the Chinese patients were equal to those of the American patients, but this may not be consistent with reality. Although the health utility value may differ due to many factors, such as psychometric and economic factors, the results of the sensitivity analysis in this model showed that utility values did not significantly affect the results of the cost-effectiveness analysis. Third, our study did not evaluate the long-term economic benefits of trilaciclib in patients with ES-SCLC. Currently, clinical research has focused primarily on the role of trilaciclib in preventing myelosuppression, and the survival outcomes of patients receiving trilaciclib remain unclear since it is not used as an antitumor therapy. The long-term benefits of trilaciclib for treating ES-SCLC patients remain uncertain and require further clinical research for evaluation. Finally, this study only assessed the use of trilaciclib in patients with ES-SCLC receiving chemotherapy combined with atezolizumab. There is a lack of clinical studies on the use of trilaciclib for the prevention of myelosuppression in SC-SCLC patients receiving chemotherapy combined with other ICIs, such as durvalumab or serplulimab. Owing to the absence of relevant outcome parameters, the cost-effectiveness of trilaciclib in patients receiving chemotherapy combined with other ICIs is unclear. However, we hypothesize that the economic evaluation of trilaciclib for the prevention of myelosuppression in patients with ES-SCLC treated with chemotherapy in combination with other ICIs is consistent with the results of this study because the cost of ICIs is high. However, this is only speculation, and proper economic analysis is needed to determine whether trilaciclib is cost effective at preventing myelosuppression when combined with other ICIs and chemotherapy.

Conclusion

This study assessed the use of trilaciclib administered before E/P/A in patients with ES-SCLC for the prevention of myelosuppression from the perspective of Chinese and US payers. This study revealed that administering trilaciclib before E/P/A is not an economic treatment strategy for ES-SCLC patients in China at the WTP threshold of $35,817.44/QALY. However, trilaciclib is economical for treating ES-SCLC patients in the US at a WTP threshold of $241,230.00/QALY.

Disclosure of conflict of interest

None.

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References

[1] Siegel RL, Miller KD, Wagle NS and Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023; 73: 17-48.

[2] Gazdar AF, Bunn PA and Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. Nat Rev Cancer 2017; 17: 725-737.

[3] Micke P, Faldum A, Metz T, Beeh KM, Bittinger F, Hengstler JG and Buhl R. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer--what limits limited disease? Lung Cancer 2002; 37: 271-276.

[4] Ni J, Zhang X, Wang H, Si X, Xu Y, Zhao J, Chen M, Zhang L and Wang M. Clinical characteristics and prognostic model for extensive-stage small cell lung cancer: a retrospective study over an 8-year period. Thorac Cancer 2022; 13: 539-548.

[5] Schwendenwein A, Megyesfalvi Z, Barany N, Valko Z, Bugyik E, Lang C, Ferencz B, Paku S, Lantos A, Fillinger J, Rezeli M, Marko-Varga G, Bogos K, Galffy G, Renyi-Vamos F, Hoda MA, Klepetko W, Hoetzenecker K, Laszlo V and Dome B. Molecular profiles of small cell lung cancer subtypes: therapeutic implications. Mol Ther Oncolytics 2021; 20: 470-483.

[6] National Comprehensive Cancer Network. 2024. Small Cell Lung Cancer Version 2.2024. Available from: https://data.stats.gov.cn/search.htm. Accessed Dec 12, 2023.

[7] Yu Y, Chen K and Fan Y. Extensive-stage small-cell lung cancer: current management and future directions. Int J Cancer 2023; 152: 2243-2256.

[8] Zhu Y, Liu K, Zhu H, Cao H and Zhou Y. Comparative efficacy and safety of novel immuno-chemotherapy for extensive-stage small-cell lung cancer: a network meta-analysis of randomized controlled trial. Ther Adv Med Oncol 2023; 15: 17588359231206147.

[9] Frampton JE. Atezolizumab: a review in extensive-stage SCLC. Drugs 2020; 80: 1587-1594.

[10] Liu SV, Reck M, Mansfield AS, Mok T, Scherpereel A, Reinmuth N, Garassino MC, De Castro Carpeno J, Califano R, Nishio M, Orlandi F, Alatorre-Alexander J, Leal T, Cheng Y, Lee JS, Lam S, McCleland M, Deng Y, Phan S and Horn L. Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). J Clin Oncol 2021; 39: 619-630.

[11] Fujimoto D, Morimoto T, Tamiya M, Hata A, Matsumoto H, Nakamura A, Yokoyama T, Taniguchi Y, Uchida J, Sato Y, Yokoi T, Tanaka H, Furuya N, Masuda T, Sakata Y, Miyauchi E, Hara S, Saito G, Miura S, Kanazu M, Yamamoto N and Akamatsu H. Outcomes of chemoimmunotherapy among patients with extensive-stage small cell lung cancer according to potential clinical trial eligibility. JAMA Netw Open 2023; 6: e230698.

[12] National Cancer Institute-Division of Cancer Treatment and Diagnosis. 2017. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_60. Accessed Dec 11, 2023.

[13] Epstein RS, Weerasinghe RK, Parrish AS, Krenitsky J, Sanborn RE and Salimi T. Real-world burden of chemotherapy-induced myelosuppression in patients with small cell lung cancer: a retrospective analysis of electronic medical data from community cancer care providers. J Med Econ 2022; 25: 108-118.

[14] Goldschmidt J, Monnette A, Shi P, Venkatasetty D, Lopez-Gonzalez L and Huang H. Burden of chemotherapy-induced myelosuppression among patients with ES-SCLC in US community oncology settings. Future Oncol 2022; 18: 3881-3894.

[15] Roskoski R Jr. Properties of FDA-approved small molecule protein kinase inhibitors: a 2023 update. Pharmacol Res 2023; 187: 106552.

[16] National drug supervision and administration of government services portal. 2022. Drug approval documents to be received information release on July 13, 2022. Available from: https://data.stats.gov.cn/easyquery.htm?cn=C01&zb=A0201&sj=2022. Accessed Dec 15, 2023.

[17] Daniel D, Kuchava V, Bondarenko I, Ivashchuk O, Reddy S, Jaal J, Kudaba I, Hart L, Matitashvili A, Pritchett Y, Morris SR, Sorrentino JA, Antal JM and Goldschmidt J. Trilaciclib prior to chemotherapy and atezolizumab in patients with newly diagnosed extensive-stage small cell lung cancer: a multicentre, randomised, double-blind, placebo-controlled Phase II trial. Int J Cancer 2021; 148: 2557-2570.

[18] Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, Mauskopf J, Mullins CD, Petrou S, Pwu RF and Staniszewska S; CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. BMJ 2022; 376: e067975.

[19] Liang X, Chen X, Li H and Li Y. Cost-effectiveness analysis of first-line serplulimab combined with chemotherapy for extensive-stage small cell lung cancer. Front Public Health 2023; 11: 1156427.

[20] Zhu Y, Liu K, Qin Q and Zhu H. Serplulimab plus chemotherapy as first-line treatment for extensive-stage small-cell lung cancer: a cost-effectiveness analysis. Front Immunol 2023; 13: 1044678.

[21] Ganti AKP, Loo BW, Bassetti M, Blakely C, Chiang A, D'Amico TA, D'Avella C, Dowlati A, Downey RJ, Edelman M, Florsheim C, Gold KA, Goldman JW, Grecula JC, Hann C, Iams W, Iyengar P, Kelly K, Khalil M, Koczywas M, Merritt RE, Mohindra N, Molina J, Moran C, Pokharel S, Puri S, Qin A, Rusthoven C, Sands J, Santana-Davila R, Shafique M, Waqar SN, Gregory KM and Hughes M. Small cell lung cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2021; 19: 1441-1464.

[22] National Bureau of Statistics of China. 2022. Gross domestic product. Available from: https://data.stats.gov.cn/search.htm. Accessed Dec 12, 2023.
[23] International Monetary Fund. 2023. GDP per capita, current prices. Available from: https://www.imf.org/external/datamapper/NGDPDPC@WEO/OEMDC/ADVEC/WEOWORLD/USA. Accessed Dec 12, 2023.
[24] Murray CJ, Evans DB, Acharya A and Baltussen RM. Development of WHO guidelines on generalized cost-effectiveness analysis. Health Econ 2000; 9: 235-251.
[25] State Administration of Foreign Exchange. 2023. Table of conversion rates of various currencies to the US dollar. Available from: https://www.safe.gov.cn/safe/gzhbdmyzslb/index.html. Accessed Dec 12, 2023.
[26] Yaozhi database. 2023. Drug bidding information. Available from: https://db.yaozh.com/yaopinzhongbiao. Accessed Dec 12, 2023.
[27] Centers for Medicare & Medicaid Services. 2023. October 2023 ASP Pricing File - Final file 092023. Available from: https://www.cms.gov/medicare/payment/part-b-drugs/asp-pricing-files. Accessed Dec 12, 2023.
[28] Abraham I, Goyal A, Deniz B, Moran D, Chioda M, MacDonald KM and Huang H. Budget impact analysis of trilaciclib for decreasing the incidence of chemotherapy-induced myelosuppression in patients with extensive-stage small cell lung cancer in the United States. J Manag Care Spec Pharm 2022; 28: 435-448.
[29] Zhao J, Qiao G, Liang Y, Li J, Hu W, Zuo X, Li J, Zhao C, Zhang X and Du S. Cost-effectiveness analysis of PEG-rhG-CSF as primary prophylaxis to chemotherapy-induced neutropenia in women with breast cancer in China: results based on real-world data. Front Pharmacol 2022; 12: 754366.
[30] Xiang G, Jiang T, Gan L, Wu Y, Zhang N, Xing H, Su H, Li Y, Peng D, Ni R and Liu Y. Cost-effectiveness of serplulimab as first-line therapy for extensive-stage small cell lung cancer in China. Front Immunol 2023; 14: 1223020.
[31] Shao T, Zhao M, Liang L and Tang W. Serplulimab plus chemotherapy vs chemotherapy for treatment of US and Chinese patients with extensive-stage small-cell lung cancer: a cost-effectiveness analysis to inform drug pricing. BioDrugs 2023; 37: 421-432.
[32] Tom's Inflation Calculator. 2022. Consumer Price Index. Available from: https://halfhill.com/inflation_js.html. Accessed Dec 12, 2023.
[33] Abraham I, Onyekwere U, Deniz B, Moran D, Chioda M, MacDonald K and Huang H. Trilaciclib and the economic value of multilineage myeloprotection from chemotherapy-induced myelosuppression among patients with extensive-stage small cell lung cancer treated with first-line chemotherapy. J Med Econ 2021; 24: 71-83.
[34] Kondo Y, Tachi T, Sakakibara T, Kato J, Kato A, Mizuno T, Miyake Y and Teramachi H. Cost-effectiveness analysis of pegfilgrastim in patients with non-small cell lung cancer receiving ramucirumab plus docetaxel in Japan. Support Care Cancer 2022; 30: 6775-6783.
[35] Weiss J, Goldschmidt J, Andric Z, Dragnev KH, Gwaltney C, Skaltsa K, Pritchett Y, Antal JM, Morris SR and Daniel D. Effects of trilaciclib on chemotherapy-induced myelosuppression and patient-reported outcomes in patients with extensive-stage small cell lung cancer: pooled results from three phase II randomized, double-blind, placebo-controlled studies. Clin Lung Cancer 2021; 22: 449-460.
[36] Cheng Y, Wu L, Huang D, Wang Q, Fan Y, Zhang X, Fan H, Yao W, Liu B, Yu G, Pan Y, Xu F, He Z, Dong X, Ma R, Min X, Ge X, Chen H, Liu Q, Hu Y, Liu Y, Yang C, Yang Y, Li X and Zhou L. Myeloprotection with trilaciclib in Chinese patients with extensive-stage small cell lung cancer receiving chemotherapy: results from a randomized, double-blind, placebo-controlled phase III study (TRACES). Lung Cancer 2024; 188: 107455.
[37] Chen H, Ma X, Liu J, Yang Y, Fang Y, Wang L, Fang J, Zhao J and Zhuo M. Clinical outcomes of atezolizumab in combination with etoposide/platinum for treatment of extensive-stage small-cell lung cancer: a real-world, multicenter, retrospective, controlled study in China. Chin J Cancer Res 2022; 34: 353-364.
[38] Messori A and Trippoli S. The results of a pharmacoeconomic study: incremental cost-effectiveness ratio versus net monetary benefit. Heart 2017; 103: 1746.
[39] TreeAge Software Inc. 2018. TreeAge Pro 2018 User's Manual. Available from: http://files.treeage.com/treeagepro/18.2.0/20180628/TP-Manual-TP2018R2.pdf. Accessed Oct 30, 2020.
[40] Zhang T, Li W, Diwu D, Chen L, Chen X and Wang H. Efficacy and safety of first-line immunotherapy plus chemotherapy in treating patients with extensive-stage small cell lung cancer: a Bayesian network meta-analysis. Front Immunol 2023; 14: 1197044.
[41] Zethraeus N, Johannesson M, Jonsson B, Lothgren M and Tambour M. Advantages of using the net-benefit approach for analysing uncertainty in economic evaluation studies. Pharmacoeconomics 2003; 21: 39-48.
[42] Zhou K, Zhou J, Huang J, Zhang N, Bai L, Yang Y and Li Q. Cost-effectiveness analysis of atezolizumab plus chemotherapy in the first-line

treatment of extensive-stage small-cell lung cancer. Lung Cancer 2019; 130: 1-4.
[43] Wang Y, Rui M, Yang L, Wang X, Shang Y, Ma A and Li H. Economic evaluation of first-line atezolizumab for extensive-stage small-cell lung cancer in the US. Front Public Health 2021; 9: 650392.
[44] Li LY, Wang H, Chen X, Li WQ and Cui JW. First-line atezolizumab plus chemotherapy in treatment of extensive small cell lung cancer: a cost-effectiveness analysis from China. Chin Med J (Engl) 2019; 132: 2790-2794.

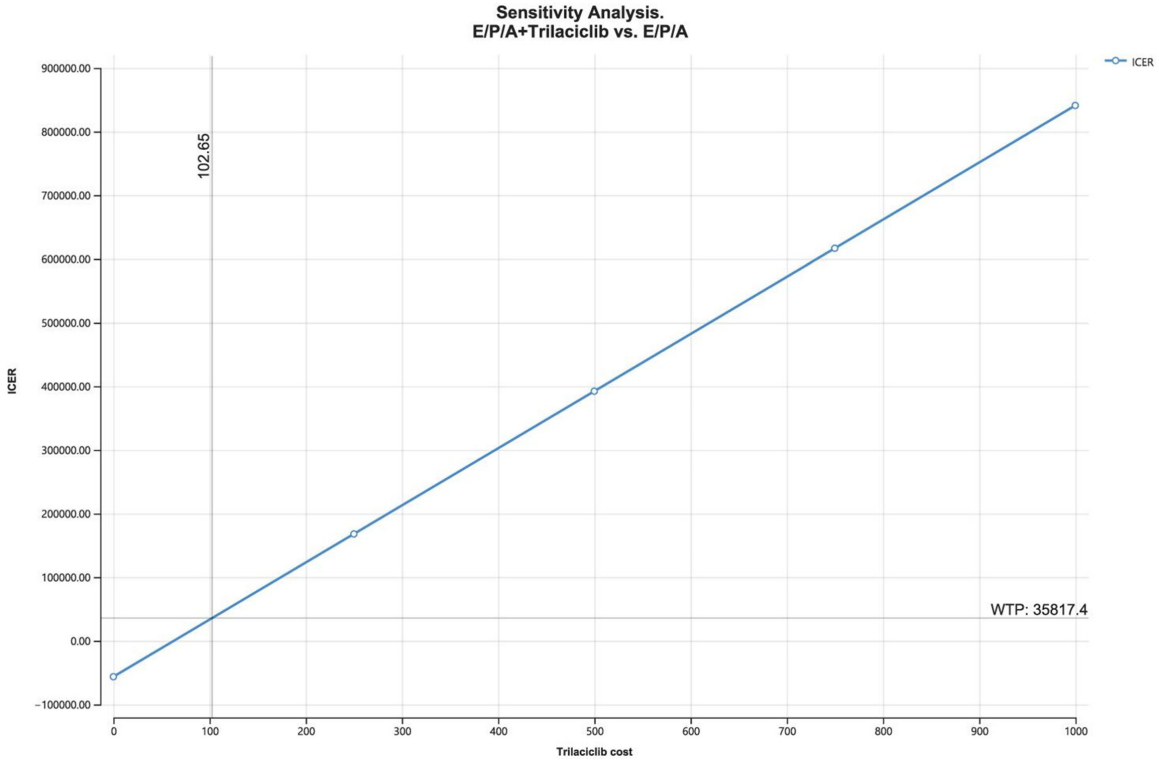

Figure S1. One-way sensitivity analysis of the cost of trilaciclib from the perspective of Chinese payers.

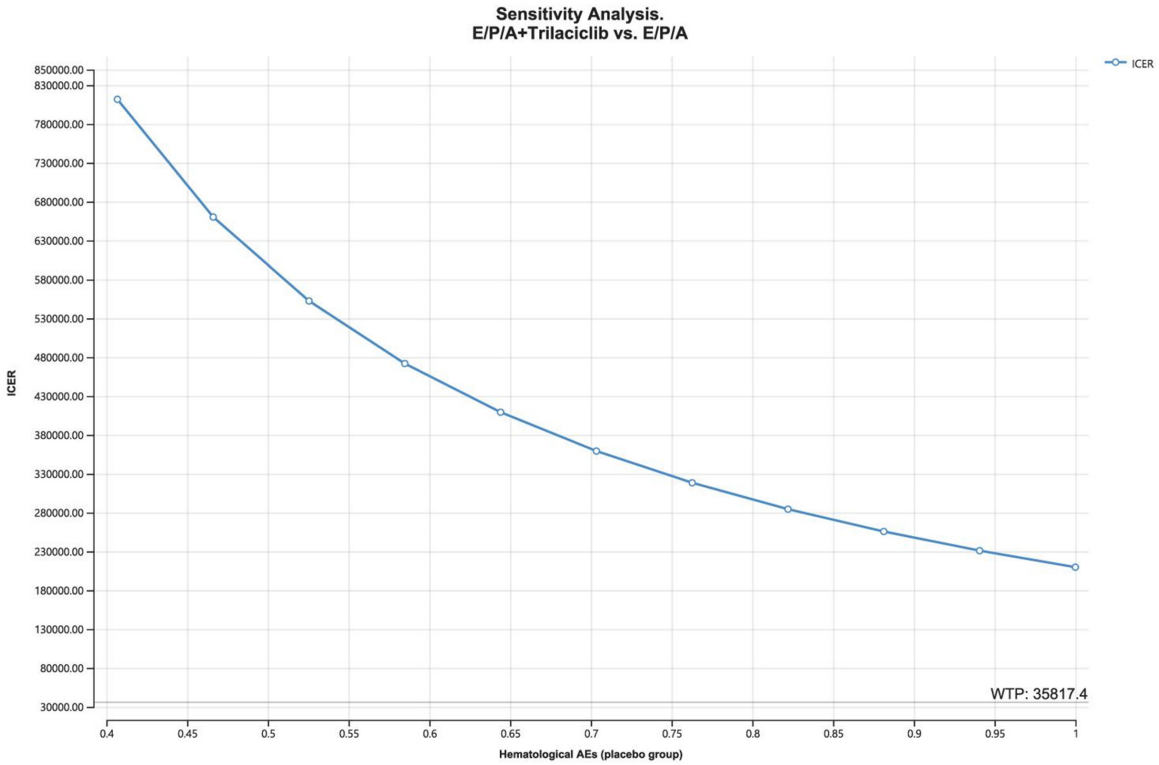

Figure S2. One-way sensitivity analysis of the probability of hematological adverse events in the placebo group from the perspective of Chinese payers.

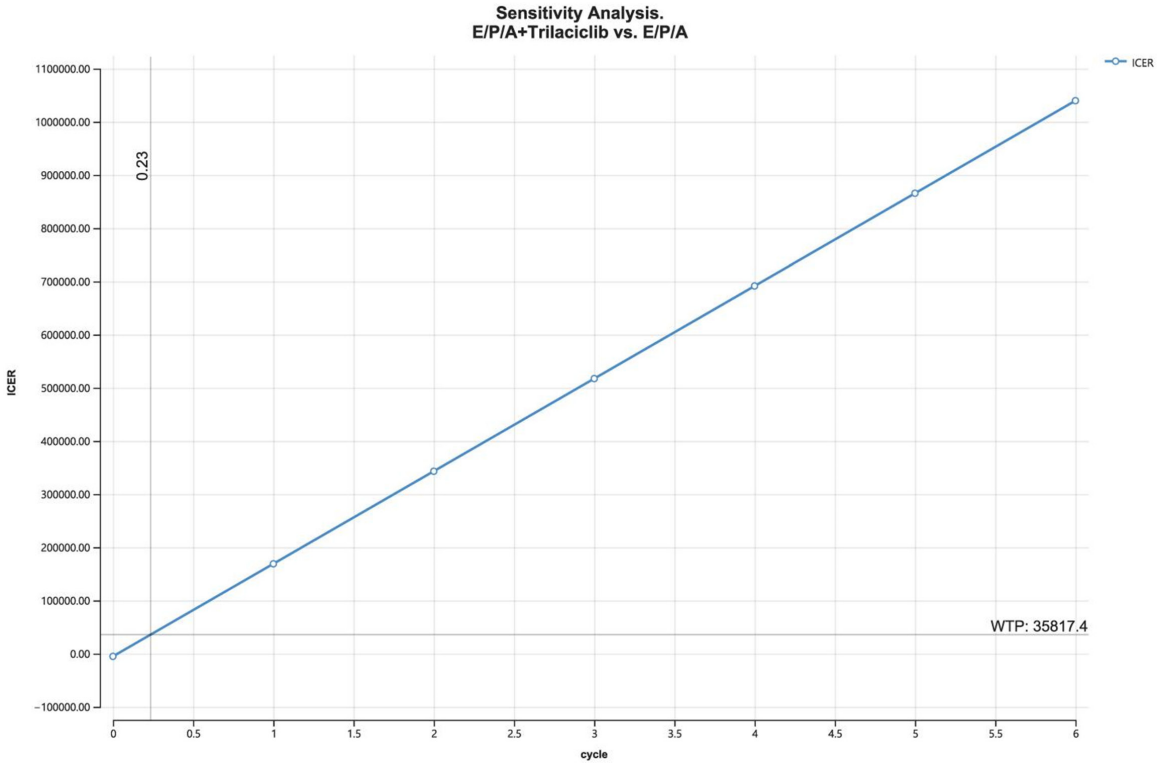

Figure S3. One-way sensitivity analysis of the average number of chemotherapy cycles from the perspective of Chinese payers.

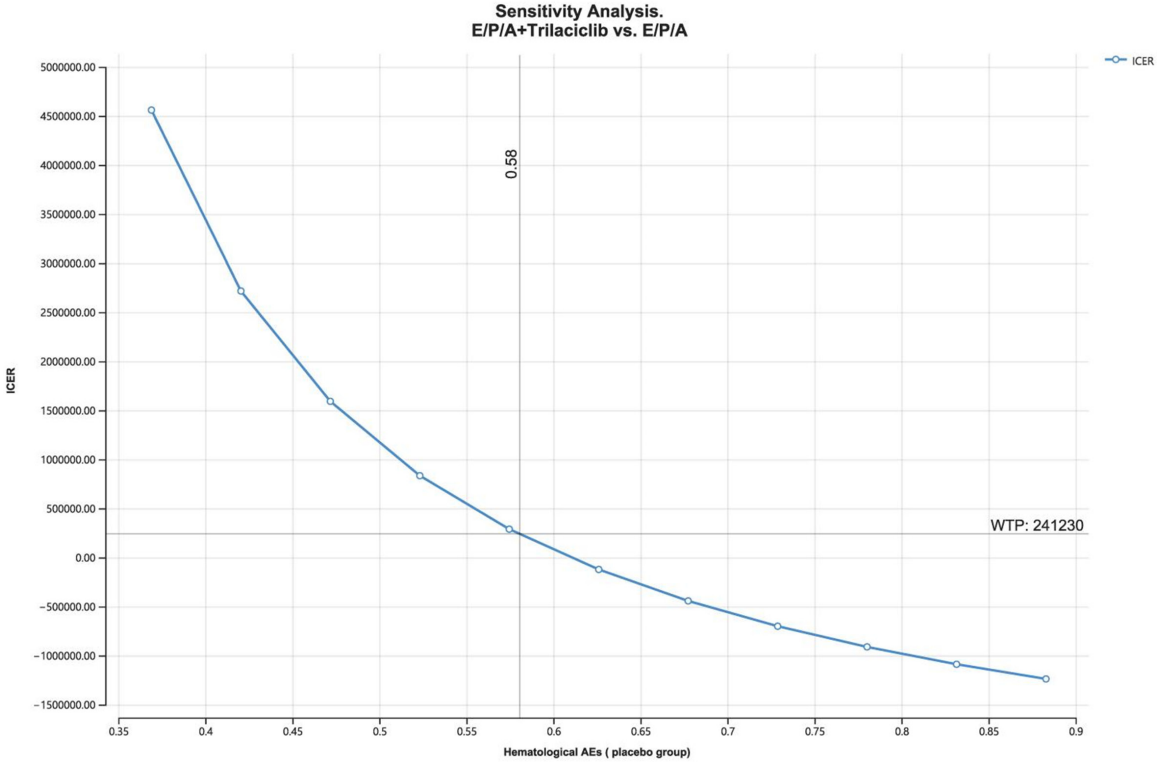

Figure S4. One-way sensitivity analysis of the probability of hematological adverse events in placebo group from the perspective of US payers.

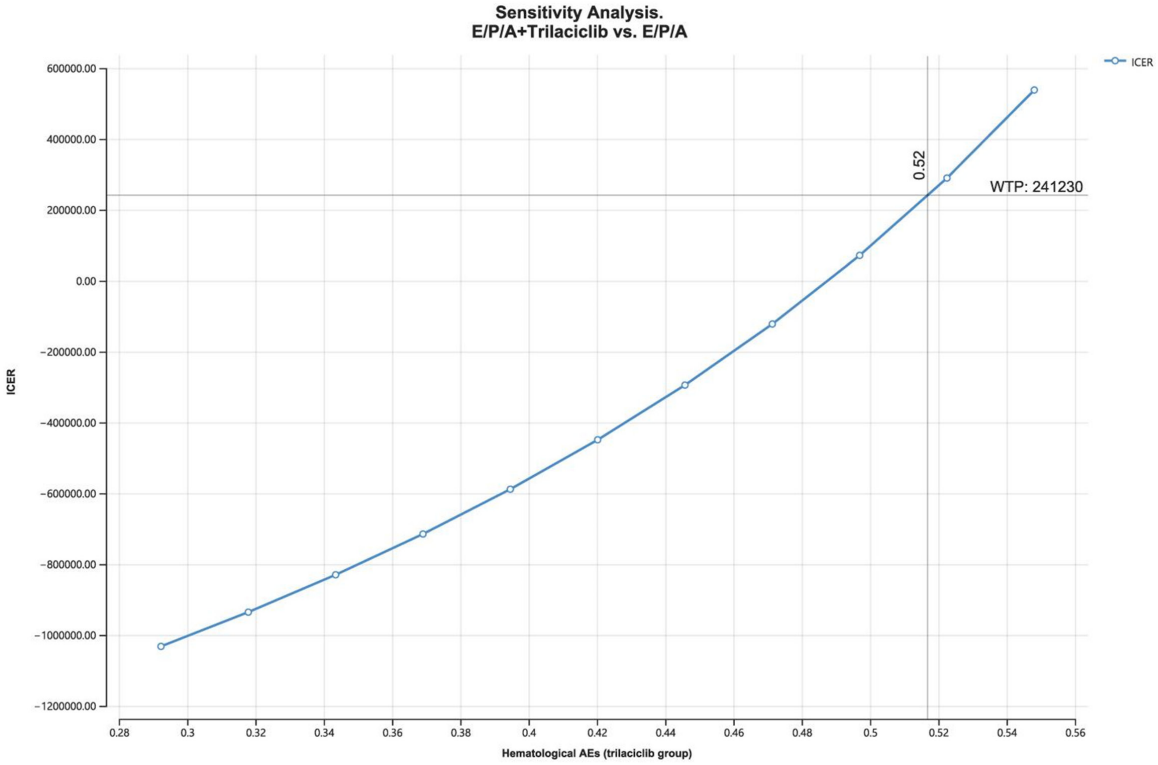

Figure S5. One-way sensitivity analysis of the probability of hematological adverse events in trilaciclib group from the perspective of US payers.