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Cost-effectiveness analysis of pembrolizumab plus chemotherapy as first-line treatment for advanced biliary tract cancer: perspectives from US and Chinese payers

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ABSTRACT

Background The KEYNOTE-966 study demonstrated that pembrolizumab combined with chemotherapy is more effective than chemotherapy alone as first-line treatment for patients with advanced biliary tract cancer (BTC). However, the cost-effectiveness of pembrolizumab combined with chemotherapy in the USA and China remains uncertain.

Objective This study aimed to evaluate the cost-effectiveness of pembrolizumab plus chemotherapy compared with placebo plus chemotherapy from the perspective of US and Chinese payers.

Design Markov models with three health states were developed to simulate the process of advanced BTC. Cost data were obtained from available databases and published literature in the US scenario, and from local institutions from the China scenario. Utility values were derived from previous studies.

Outcome measures Primary outcomes included quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs).

Results In the US scenario, pembrolizumab plus chemotherapy increased costs by US$97,222.13, compared with chemotherapy alone, with a gain of 0.12 QALYs, resulting in an ICER of US$810 184.42 per QALY. In the China scenario, the ICER was $360 933.50 per QALY. Sensitivity analyses indicated the costs of pembrolizumab had the greatest impact on the model in both scenarios. Further analyses suggested that the optimal price of pembrolizumab in the USA would be nearly US$10.33/mg, while a price reduction of over 90% would be required for the combined therapy to be cost-effective for patients in China.

Conclusion Based on the willingness-to-pay threshold set at three times the gross domestic product per capita, pembrolizumab plus chemotherapy is not a cost-effective option for patients with advanced BTC in either the USA or China. Significant price reduction for pembrolizumab may be necessary to achieve an acceptable ICER.

Trial registration number NCT04003636; postresults.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A cost-effectiveness analysis was performed from the perspective of US and Chinese payers comparing pembrolizumab plus chemotherapy compared with placebo plus chemotherapy.
⇒ The framework of this model is aligned with the Markov model.
⇒ One-way sensitivity analyses revealed that the price of pembrolizumab significantly impacts incremental cost-effectiveness ratios.
⇒ This analysis was limited, as some variables in the models were derived from published studies, which may not fully capture real-world conditions.
⇒ Costs can vary between medical centres and countries, potentially affecting the generalisability of our findings, compounded by the lack of independent model validation.

INTRODUCTION

Biliary tract cancer (BTC) includes intrahepatic or extrahepatic cholangiocarcinoma cancer, gallbladder cancer and ampullary cancer.[1] With an incidence rate of fewer than six cases per 100 000 individuals,[2] BTC is considered a low-incidence cancer. However, it has a poor prognosis, with an estimated 5-year overall survival (OS) rate of <20%.[3]

Despite significant advancements in various cancer treatments over the past decades, progress in treating advanced BTC has stagnated. For over 10 years, the standard first-line therapy for advanced BTC has been the chemotherapy regimen combining gemcitabine and cisplatin.[4] However, this treatment faces many challenges, including drug resistance and recurrence in the majority of patients. Previous study indicated that BTC has immunogenic characteristics,[5] prompting efforts to explore novel treatments. A phase 2 study demonstrated that adding durvalumab, a humanised monoclonal antiprogrammed death ligand 1 (PD-L1) antibody, to chemotherapy significantly improved survival rates for patients with advanced BTC, achieving

an objective response rate of 72%.[6] Further phase 3 trial (TOPAZ-1, NCT03875235) corroborated these findings, showing that durvalumab combined with chemotherapy significantly prolonged the progression-free survival (PFS) (7.2 vs 5.7 months; HR=0.75; p=0.001) and OS (12.9 vs 11.3 months; HR=0.76).[7] Consequently, the FDA approved durvalumab plus gemcitabine and cisplatin as first-line treatment for advanced BTC in 2022.[8]

Pembrolizumab, an anti-PD-1 monoclonal antibody, has a broad range of indications, including non-squamous non-small-cell lung cancer (NSCLC), extensive-stage small-cell lung cancer (ES-SCLC), advanced triple-negative breast cancer and gastro-oesophageal junction cancer.[9] Recently, the KEYNOTE-966 study evaluated its combination with gemcitabine and cisplatin as first-line treatment for advanced BTC. The results confirmed the superior efficacy of the combined therapy, significantly prolonged median OS (12.7 vs 10.9 months; p=0.0034) and median PFS (6.5 vs 5.6 months; p=0.023) compared with the competitor. The adverse events (AEs) were manageable.[10] Thus, pembrolizumab plus chemotherapy may represent a new treatment option for patients with previously untreated metastatic or unresectable BTC.

However, the growing field of immunotherapy has raised concerns about its economic value. Higher medical costs often limit the generalisability of immune checkpoint inhibitors. Previous studies have suggested that durvalumab combined with chemotherapy was not cost-effective as first-line treatment for BTC compared with chemotherapy alone.[11 12] Therefore, this study aims to evaluate whether pembrolizumab plus chemotherapy is cost-effective for patients with advanced BTC in the USA and China.

MATERIAL AND METHODS

Clinical inputs

Markov models were developed using medical data from the KEYNOTE-966 study.[10] In the KEYNOTE-966 study, patients with untreated BTC were randomised to receive gemcitabine and cisplatin plus pembrolizumab or placebo. Pembrolizumab or placebo was administrated at 200 mg every 3 weeks (maximum of 35 cycles) until disease progression or other specified conditions. All patients received gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) on days 1 and 8 of each 3-week cycle. Cisplatin was limited to eight cycles, while gemcitabine has no maximum duration. The age in the pembrolizumab plus gemcitabine and cisplatin was 64.0 (range 57.0–71.0) and in the placebo plus gemcitabine and cisplatin was 63.0 (range 55.0–70.0). Regular efficacy and safety assessments were conducted, with similar incidences of grade ≥3 AEs in both groups. Crossover was not permitted after disease progression, and 253 (47%) of 533 participants in the pembrolizumab group and 261 (49%) of 536 participants in the placebo group received ≥1 subsequent anticancer therapy. FOLFOX (fluorouracil and oxaliplatin)

Table 1 Costs and health utilities

Variables	USA				China			
	Value	Range (min-max)	Distribution	Ref	Value	Range(min-max)	Distribution	Ref
Cost of drugs ($/mg)								
Pembrolizumab	55.417	44.3336–66.5004	Gamma	15	25.416	20.3328–30.4992	Gamma	a
Gemcitabine	0.017	0.0136–0.0204	Gamma	15	0.048	0.0384–0.0576	Gamma	a
Cisplatin	0.169	0.1352–0.2028	Gamma	15	0.090	0.072–0.108	Gamma	a
Fluorouracil	0.005	0.004–0.006	Gamma	15	0.017	0.0136–0.0204	Gamma	a
Calcium folinate	0.068	0.0544–0.0816	Gamma	15	0.022	0.0176–0.0264	Gamma	a
Oxaliplatin	0.148	0.1184–0.1776	Gamma	15	0.672	0.5376–0.8064	Gamma	a
Cost of main AEs								
Neutropenia/leucopenia	986.58	789.264–1183.896	Gamma	17	17.604	14.0832–21.1248	Gamma	a
Anaemia	1370.55	1096.44–1644.66	Gamma	17	34.255	27.404–41.106	Gamma	a
Thrombocytopenia	1008	806.4–1209.6	Gamma	17	335.745	268.596–402.894	Gamma	a
Cost of test per cycle ($)	732	585.6–878.4	Gamma	16	278.014	222.4112–333.6168	Gamma	a
Cost of best supportive care per cycle ($)	637	509.6–794.4	Gamma	18	25.532	20.4256–30.6384	Gamma	a
Utility score								
PFS	0.76	0.61–0.91	Beta	22	0.76	0.61–0.91	Beta	22
PD	0.68	0.54–0.82	Beta	22	0.68	0.54–0.82	Beta	22
Death	0	0	Beta	22	0	0	Beta	22

a, from local hospital.
AEs, adverse events; PFS, progression-free survival; PD, progressive disease.

was assumed as the second-line treatment for advanced BTC.[13]

Individual survival data were obtained from the Kaplan-Meier survival curves in the KEYNOTE-966 study. Due to the challenges associated with long-term tracking in clinical trials and the limited follow-up period to evaluate the impact of drug administration on the target population, this study employed Plot Digitizer software (V.2.6.8) to extract individual patient data from the Kaplan-Meier (K-M) curves for PFS and OS in the KEYNOTE-966 trial. Weibull survival models were constructed and validated using R software (online supplemental figure 1), following established methods from previous studies.[14]

Ethics statement

All data were collected from publicly accessible sources and analysed in compliance with relevant institutional guidelines, and no ethics approval was required for this study.

Resources of costs and utility

Direct medical costs included drug costs, AE management, supportive care, treatments for PD and monitoring administration. US drug prices were sourced from a public database,[15] while costs of AEs, monitoring and supportive care were obtained from previous studies.[16–18] In China, direct medical costs were calculated from data provided by West China Hospital. The costs collected at West China Hospital encompassed fees for treatment medications, imaging (CT), routine blood tests (including complete blood count, biochemistry and urinalysis), ECGs and other related services. Dosages were based on body surface area (BSA), with published data indicating BSA of 1.84 m^2 for US patients and 1.72 m^2 for Chinese patients.[19 20] Costs in China were converted to US dollars ($1=RMB 7.05 as of 23 May 2023).

Health utility values, although measured using the European Organisation for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire in the original study, were not disclosed. Therefore, published data were used to assign a utility score of 0.76 for PFS, 0.68 for PD and 0 for death[12 21] (table 1).

Models structure

The Weibull survival models compared the costs and quality-adjusted life years (QALYs) of two treatments: pembrolizumab plus chemotherapy versus placebo plus chemotherapy. The models included three health states: PFS, progressive disease (PD) and death (figure 1). Each treatment cycle was set at 3 weeks, and a 10-year time horizon with half-cycle correction was applied based on the previous data about BTC.[6 7] The analyses were performed using TreeAge Pro 2022 and R software (V.3.5.2) (table 2).

Statistical analysis

Incremental cost-effectiveness ratios (ICERs) were calculated from the perspective of US and Chinese payers. Costs and QALYs were discounted at an annual rate of 3%. The willingness-to-pay (WTP) threshold was set at three

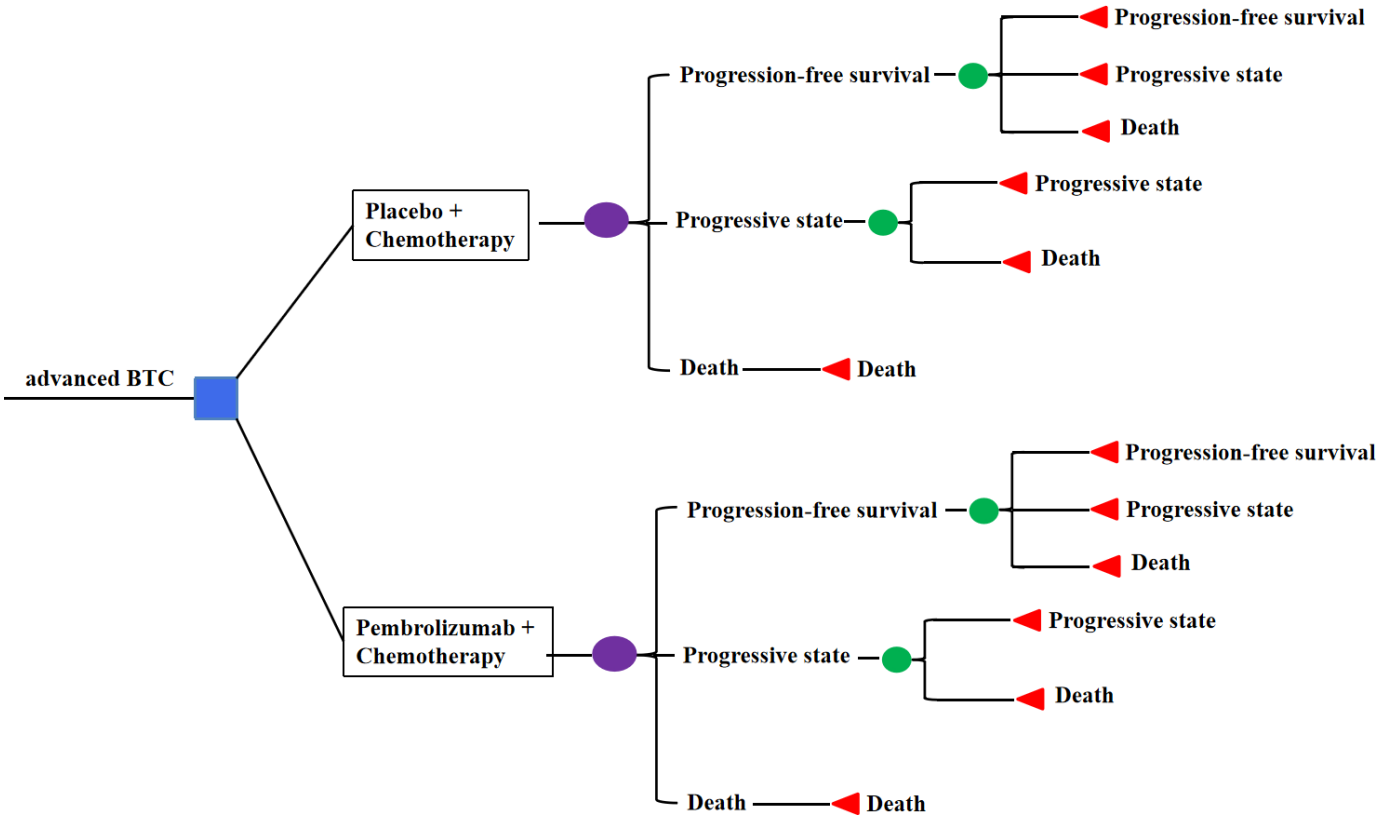

Figure 1 Markov models. BTC, biliary tract cancer.

Table 2 Parameters of survival distribution

Parameters	Placebo+ chemotherapy	Pembrolizumab+ chemotherapy
Weibull OS model		
Intercept	2.753	2.882
Log (scale)	−0.228	−0.268
Gamma	1.256	1.308
Lambda	0.032	0.023
Weibull PFS model		
Intercept	2.066	2.185
Log (scale)	−0.177	−0.120
Gamma	1.193	1.128
Lambda	0.085	0.085

OS, overall survival; PFS, progression-free survival

times the gross domestic product per capita, resulting in US$210,746/QALY for the USA and $37,669/QALY for China.[22] A cost-threshold analysis was conducted to identify the cost of pembrolizumab at which it would be considered cost-effective. One-way sensitivity analyses were conducted with a 20% range to explore the influence of variables. Probabilistic sensitivity analysis was performed using Monte Carlo simulation of 1000 iterations, and the results were presented as cost-effectiveness acceptability curves, indicating that 50% of people would choose pembrolizumab plus chemotherapy.

Patients and public involvement

Patients and the public were not involved in the design, planning or execution of this study.

RESULTS

In the base case, pembrolizumab plus chemotherapy provided an additional 0.12 QALYs compared with chemotherapy alone. The treatment increased costs by US$97 222.13 in the US and $43 312.02 in China, resulting in ICERs of US$810 184.42 and $360 933.50 per QALY, respectively. These ICERs exceed the predefined thresholds for both countries (table 3). Acceptability curves further indicated that within the set thresholds, pembrolizumab plus chemotherapy is not cost-effective. However, if the WTP threshold exceeds US$800,000/QALY in the USA, 50% of patients would opt for pembrolizumab plus chemotherapy, while the remaining 50% would choose chemotherapy alone (figure 2).

One-way sensitivity analyses, illustrated with tornado diagrams (figure 3), revealed that the cost of pembrolizumab has the greatest impact on the models, followed by the utility score of PFS and PD, and cost of testing. In the USA, the cost of best supportive care ranked fifth in impact, whereas in China, the cost of chemotherapy held the fifth rank. Other parameters also significantly influenced the ICERs. Given that the current price of pembrolizumab does not render the combined therapy cost-effective, further one-way sensitivity analyses were conducted to

Table 3 Cost-effectiveness analysis

Variables	USA		China	
	Placebo+chemotherapy	Pembrolizumab+chemotherapy	Placebo+chemotherapy	Pembrolizumab+chemotherapy
Cost ($)				
PFS state	35 359.11	132 519.10	6373.2	49 541.06
PD state	582.48	644.62	1351.4	1495.56
Total costs	35 941.59	133 163.72	7724.6	51 036.62
Incremental costs		97 222.13		43 312.02
Effectiveness (QALYs)				
PFS state	0.46	0.53	0.46	0.53
PD state	0.38	0.43	0.38	0.43
Total effectiveness	0.84	0.96	0.84	0.96
Incremental effectiveness		0.12		0.12
ICER ($/QALY)		810 184.42		360 933.50

PFS, progression-free state; PD, progressive disease; QALYs, quality adjusted-life years; ICER, incremental cost-effectiveness ratio

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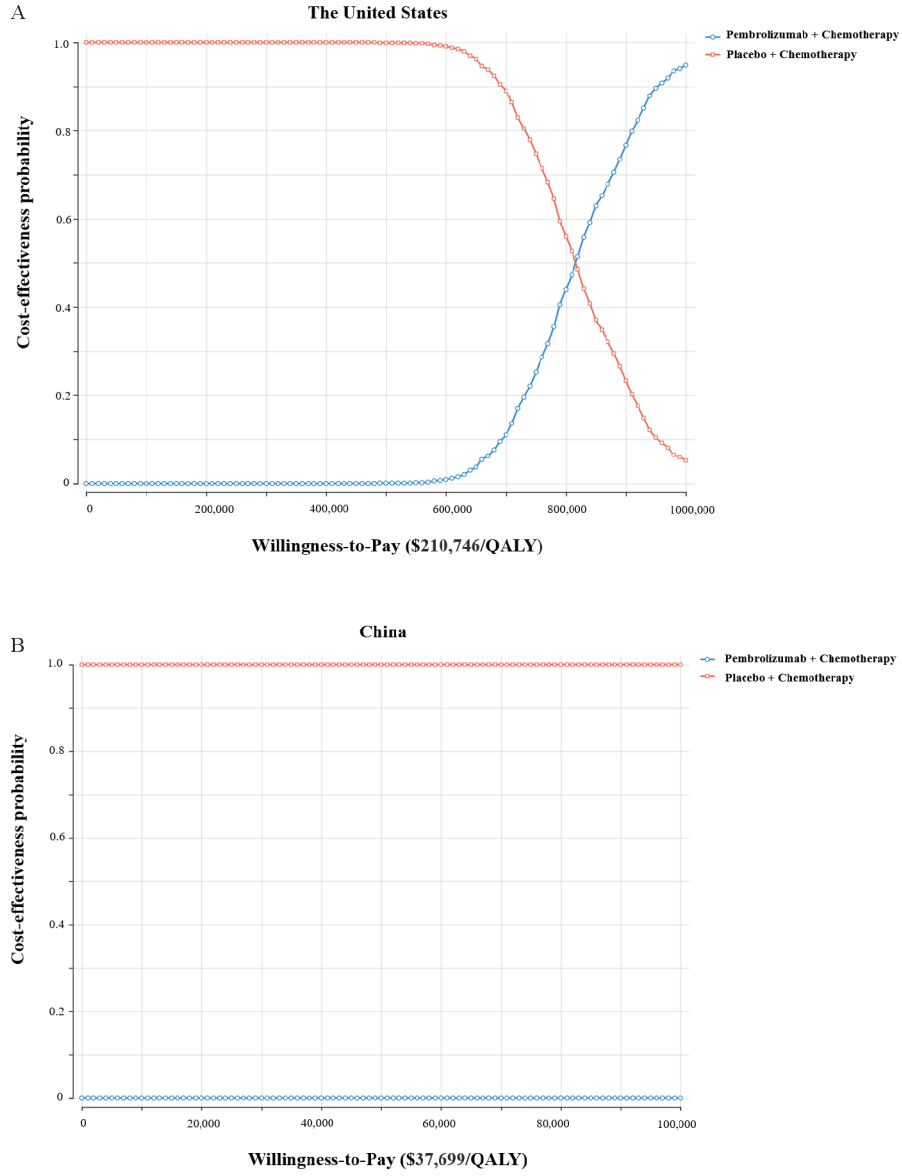

Figure 2 Cost-effectiveness acceptability curves. (A) The US scenario and (B) China scenario. QLAY, quality-adjusted life year.

determine its optimal price in both scenarios. The results suggested that in the USA, pembrolizumab plus chemotherapy could be cost-effective if the price of pembrolizumab is set at nearly $10.33/mg. In China, a price reduction of over 90% would be necessary to achieve an acceptable ICER. Incremental cost scatter plots indicated that all Monte Carlo simulation results were distributed above the WTP line, demonstrating that while pembrolizumab plus chemotherapy leads to better QALY, it also incurs higher costs (online supplemental figure 2).

DISCUSSION

This study evaluated the cost-effectiveness of pembrolizumab plus chemotherapy versus chemotherapy alone in patients with advanced BTC from the perspectives of US and Chinese payers. The findings indicated that the combined therapy significantly increased costs while providing only limited additional QALYs, resulting in ICERs of US$810,184.42/QALY in the USA and $360,933.50/QALY in China. The ICERs exceeded the predefined WTP thresholds, making the combined therapy economically unattractive. The optimal price for pembrolizumab to achieve cost-effectiveness was approximately US$10.33/mg in the USA and required over a 90% price reduction in China.

Despite rapid advancements in treatments for other cancer types, progress in medical oncology for advanced BTC has been slow, with gemcitabine and cisplatin remaining the standard first-line therapy for over a decade.[4] Previous cost-effectiveness analyses showed mixed results: Roth and Carlson found that cisplatin plus gemcitabine had an ICER of US$59 480 compared with gemcitabine monotherapy, making it economically attractive from the US societal perspective.[23] In contrast, Tsukiyama *et al* suggested that gemcitabine monotherapy was more cost-effective than its combination with cisplatin

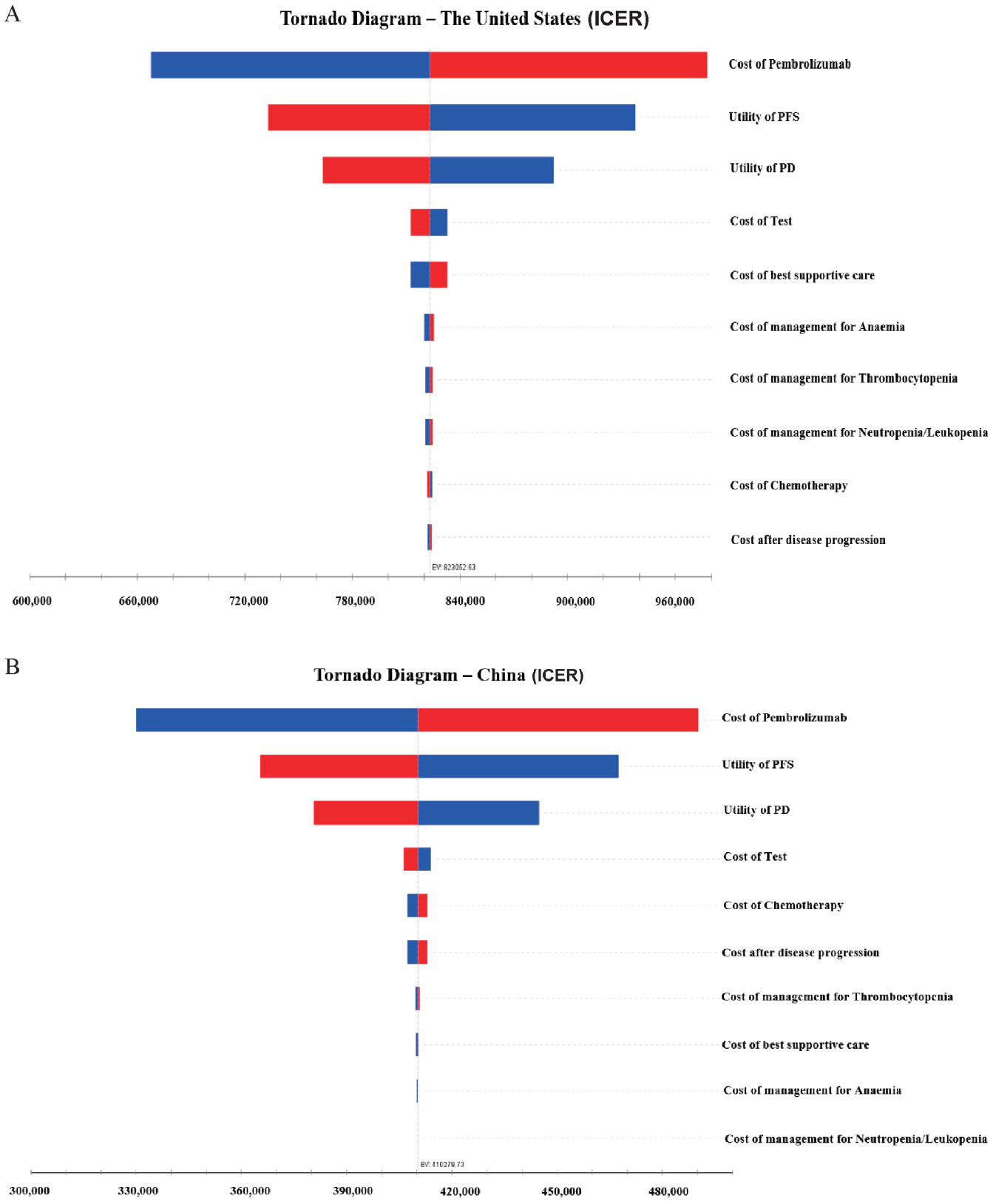

Figure 3 Tornado diagram of the one-way sensitivity analysis. (A) The USA scenario (B) China scenario. ICER, incremental cost-effectiveness ratio.

from the perspective of Japanese healthcare payers.[24] These disparities likely stem from differences in perspectives and included costs.

With the advent of immunotherapy, durvalumab emerged as a promising treatment for advanced BTC. The TOPAZ-1 study demonstrates the superior survival

benefits of durvalumab plus chemotherapy.[6 7] However, economic evaluations by Ye *et al* and Zhao *et al* indicated that durvalumab combined with chemotherapy was not cost-effective, with ICERs of US$381,864.39/QALY in the USA and $367,608.51/QALY in China.[11 12]

Pembrolizumab, although widely used for various cancers, has not been extensively studied for its economic value in advanced BTC. Studies on other cancers have shown similar economic challenges. For instance, Wan *et al* found that pembrolizumab plus standard chemotherapy for NSCLC was not cost-effective from the perspectives of US and Chinese payers.[16] Similar conclusions were drawn for other cancers, such as ES-SCLC and NSCLC, where the high cost of pembrolizumab significantly impacted ICERs.[25 26] Our one-way sensitivity analyses revealed that the price of pembrolizumab significantly impacts ICERs, aligning with findings from previous studies. Evidence suggests that traditional chemotherapy, with or without best supportive care, remains cost-effective for patients with relapsed SCLC under the National Health Service perspective.[27 28] This underscores the high cost of immunotherapy as a major factor limiting its clinical application.

The cost-effectiveness of pembrolizumab in digestive cancers remains controversial. For oesophageal cancer, studies indicated that pembrolizumab is not cost-effective compared with physician-chosen treatment like paclitaxel, docetaxel or irinotecan, from both Chinese and US perspectives.[29 30] In contrast, pembrolizumab was found to be cost-effective for metastatic colorectal cancer with high microsatellite instability (MSI-H), based on data from the KEYNOTE-177 trial.[31 32] These differences highlight the importance of predictive biomarkers in assessing the economic value of immunotherapies.

Subgroup cost-effectiveness analyses based on predictive biomarkers, such as PD-L1 combined positive score (CPS), have yielded unremarkable results. For example, Zhu *et al* found that pembrolizumab combined with chemotherapy for ES-SCLC was not cost-effective regardless of CPS.[33] Another study indicated that atezolizumab plus chemotherapy for metastatic non-squamous NSCLC also exceeded WTP thresholds across all subgroups.[34] Although the KEYNOTE-966 study assessed treatment effects based on various stratifications, specific survival data for subgroups were not provided. Future data releases could enable more detailed subgroup analyses.

Our sensitivity analyses suggest that significantly reducing the price of pembrolizumab could make the combined treatment cost-effective in China. Recently, China has implemented measures to reduce drug costs, such as decreasing the prices of domestic PD-1 inhibitors by over 60% through medical insurance and offering patient assistance programmes for imported drugs. For instance, eligible patients receiving pembrolizumab might pay for the first two cycles and receive subsequent cycles for free (2+2 and 2+X plans), significantly reducing out-of-pocket expenses by more than 85%. If approved for advanced BTC by the Chinese National Medical Products Administration, these measures could substantially alleviate the financial burden on patients. Additionally, evaluating Chinese domestic PD-1 inhibitors for advanced BTC may provide lower-cost alternatives.

This study has several limitations. Some variables in the models were derived from published studies, which may not fully reflect real-world scenarios. For instance, using published utility scores, pembrolizumab plus chemotherapy was estimated to provide only minor additional QALYs, potentially contributing to the negative results. Additionally, there are multiple subsequent treatments, such as irinotecan and regorafenib, which could affect the results due to cost variations. However, one-way sensitivity analyses with a ±20% range have been used to reduce model uncertainty. Also, costs often vary across medical centres and countries, which may affect the generalisability of our findings, compounded by the lack of independent model validation. Additionally, we only calculated the management costs for grade ≥3 haematotoxicity, as the costs for other grade ≥3 AEs are typically lower. Despite these limitations, this is the first analysis to evaluate the cost-effectiveness of pembrolizumab plus chemotherapy for advanced BTC from the perspectives of US and Chinese payers.

In conclusion, pembrolizumab plus chemotherapy is not cost-effective as a first-line treatment for advanced BTC from the perspectives of US and Chinese payers. Reducing the acquisition cost of pembrolizumab could enhance its economic viability compared with traditional chemotherapy alone.

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Patient consent for publication Not applicable.

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