BMJ Open

Cost-effectiveness of atezolizumab plus bevacizumab versus sorafenib as first-line therapy in unresectable hepatocellular carcinoma in the US and Chinese setting: a modelling comparison study

Lulu Liu,[1,2] Lei Wang,[3] Yiling Ding,[1] Qilin Zhang ,[4] Yamin Shu[1]

To cite: Liu L, Wang L, Ding Y, *et al*. Cost-effectiveness of atezolizumab plus bevacizumab versus sorafenib as first-line therapy in unresectable hepatocellular carcinoma in the US and Chinese setting: a modelling comparison study. *BMJ Open* 2025;**15**:e094804. doi:10.1136/bmjopen-2024-094804

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-094804).

LL and LW contributed equally.

Received 09 October 2024
Accepted 05 February 2025

For numbered affiliations see end of article.

Correspondence to
Dr Qilin Zhang;
qilinzhang88@163.com and
Yamin Shu;
shuyamin1990hust@163.com

ABSTRACT

Objective Atezolizumab plus bevacizumab demonstrates a significant improvement in overall survival and progression-free survival compared with sorafenib in patients with unresectable hepatocellular carcinoma (HCC). The combined usage of these two medications could result in substantial consumption of resources, primarily due to their exceptionally high costs. The current study aims to evaluate the cost-effectiveness of atezolizumab plus bevacizumab as a first-line treatment for advanced HCC from the perspective of payers in developed and developing countries.

Design A partitioned survival model was constructed to evaluate the cost-effectiveness of atezolizumab plus bevacizumab versus sorafenib as a first-line treatment for advanced HCC. The efficacy and safety data incorporated within the model were derived from the IMbrave150 trial. Costs and utilities were extracted from published sources.

Interventions Atezolizumab plus bevacizumab versus sorafenib.

Outcome measures Estimates were calculated for costs, life-years, quality-adjusted life-years (QALYs), incremental cost-effectiveness ratio (ICER) for both treatment strategies. One-way sensitivity, probabilistic sensitivity, expected value of perfect information (EVPI), subgroup and scenario analyses were conducted.

Results The combination therapy of atezolizumab and bevacizumab results in an additional 0.72 life-years/0.57 QALYs in the USA and 0.64 life-years/0.47 QALYs in China compared with standard sorafenib treatment, although with a significant increase in costs, yielding an average ICER of US$253 247.07/QALY in the USA and US$181 552.71/QALY in China. The probability sensitivity analysis indicated that atezolizumab plus bevacizumab demonstrated a 13.60% likelihood of cost-effectiveness in the USA, whereas this likelihood is negligible (0%) in China. The expected value of uncertainty, as quantified by the EVPI, was estimated at approximately US$3658.41/patient in the USA and US$0/patient in China. The ICER was most sensitive to the cost of subsequent treatment in the USA, and most sensitive to the cost of atezolizumab in China. In scenario analyses, the atezolizumab plus bevacizumab treatment becomes favourable when the cost of atezolizumab decreases to 67.85% and 18.45% of its original price in the USA and China, respectively.

Conclusions The atezolizumab plus bevacizumab is unlikely to be cost-effective compared with sorafenib for patients with unresectable HCC in the context of the USA and China. The implementation of significant reductions in drug prices may render the treatment economically viable.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A partitioned survival model and Markov model were developed in Microsoft Excel, providing enhanced transparency in data calculation and increased customisation options compared with TreeAge.
⇒ The expected value of perfect information was computed across various scenarios to mitigate uncertainty.
⇒ To examine the economic outcome uncertainties arising from subpopulations, subgroup analyses were conducted by varying the HRs.
⇒ The utilisation of parametric survival extrapolation based on the IMbrave150 trial may introduce bias and uncertainty into the findings.

INTRODUCTION

Globally, hepatocellular carcinoma (HCC), which is the predominant histological subtype among liver cancers and comprises over 80% of primary cases, ranks as the third most common cause of cancer-related deaths.[1] The majority of patients with HCC are detected in the advanced stage, for whom the 5-year survival proportion is lower than 10%.[2 3] Consequently, these patients have failed to qualify for several local treatment options, including hepatectomy, local ablation and liver transplantation. Statistical data shows that in the USA, the healthcare expenditure for treating HCC amounts to

US$405 million and is escalating annually at a pace of 5.4%.[4] An in-depth survey and comprehensive analysis of patients with liver cancer across 13 provinces in China during the period from 2012 to 2014 revealed that the average annual direct medical expenditure per patient was US$6664, imposing a significant social and economic burden.[5] In the past 10 years, the advent of novel agents such as first-line targeted therapies centred around sorafenib and lenvatinib has notably enhanced the prognoses for patients with advanced HCC, lengthening the median overall survival (OS) from the previous 4–8 months to the current 10–15 months.[6 7] Nevertheless, the available treatment alternatives for advanced HCC are still restricted, and the disease prognosis is unfavourable.

At present, immune checkpoint inhibitors (ICIs) have ushered in a new phase in the treatment of advanced HCC. The combined strategies of ICIs with other agents, for instance, the combination of anti-programmed cell death-ligand 1 and anti-angiogenic molecular targeted therapy or the combination with anti-cytotoxic T lymphocyte-associated antigen-4, have demonstrated promising results in clinical trials.[8 9] In 2020, the open-label, phase 3 randomised clinical trial named IMbrave150 (NCT03434379) assessed the effectiveness and safety of the combination of atezolizumab and bevacizumab as opposed to sorafenib in the treatment of advanced unresectable HCC.[10] Subsequently, although several economic studies evaluated the cost-effectiveness of atezolizumab plus bevacizumab versus sorafenib as a first-line therapy for advanced HCC, the median OS was not reached.[11 12] Recently, a study reported an updated descriptive analysis of OS and other efficacy and safety data from IMbrave150 after the primary analysis.[13] The results revealed that after a median 15.6 months of follow-up, atezolizumab plus bevacizumab significantly prolonged the median OS (19.2 months vs 13.4 months; HR 0.66; 95% CI, 0.52 to 0.85, p<0.001) and progression-free survival (PFS) (6.9 months vs 4.3 months; HR, 0.65; 95% CI, 0.53 to 0.81) in comparison with sorafenib.[13] The rate of treatment-related grade 3/4 adverse events (AEs) was comparable between the two groups (43% vs 46%). Consequently, atezolizumab plus bevacizumab has become a new first-line standard of care and is recommended both by the latest National Comprehensive Cancer Network and the Chinese Society of Clinical Oncology clinical practice guidelines for advanced HCC.[14 15] Based on the latest data, this study aimed to assess the cost-effectiveness of atezolizumab plus bevacizumab versus sorafenib as the first-line treatment for patients with unresectable HCC, considering the healthcare settings of the USA (a developed country) and China (a developing country), respectively.

METHODS

Analytical overview

The target patient population for this analysis consisted of patients with previously untreated and unresectable HCC, in accordance with the patient definitions outlined in the IMbrave150 trial.[10 13] A partitioned survival model with three health states was employed to conduct the economic analyses from the perspectives of the healthcare systems in the USA and China (figure 1). In the model, patients were classified into three mutually exclusive health states according to the results of the IMbrave150 trial:[10 13] PFS, progressed disease (PD) and death. The proportion alive with PFS was estimated by the area under the PFS curves, and the proportion of PD was estimated by the difference between the OS and PFS curves.[12] As the OS curves represented the proportion of alive patients, the proportion of dead patients simply equalled 1–OS.[12] The lifetime horizon (from the mean age of patients to the time when 99% of patients died in the model) and 1 week cycle length were adopted in this model because HCC would last a lifetime. One-week cycle length allowed for a more precise estimation of the cumulative costs and benefits as the model updated through each week of the lifetime horizon. This study followed the reporting guideline of Consolidated Health Economic Evaluation Reporting Standards (2022).[16] As the present study relied on published literature and on modelling techniques, Ethics Committee approval was not required.

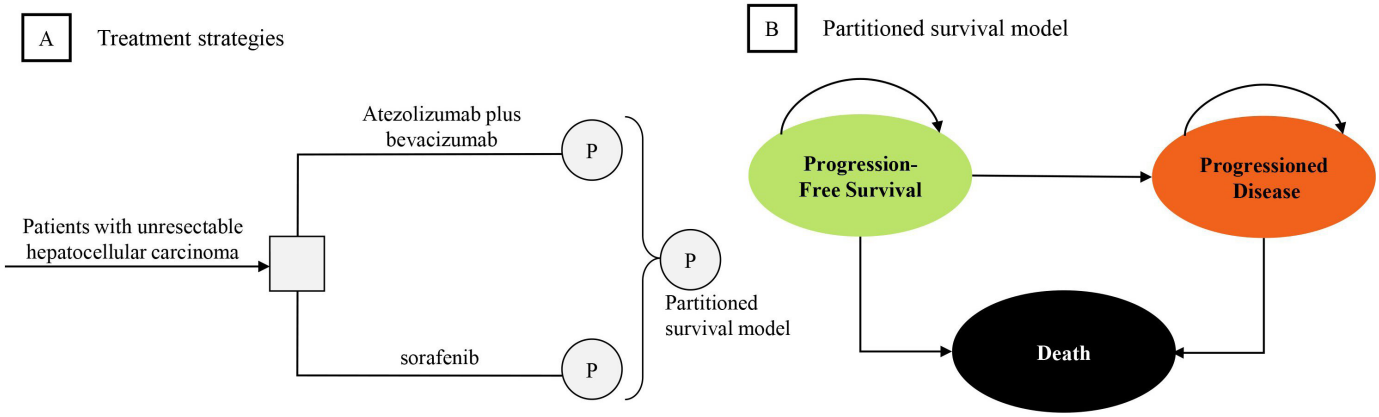

Figure 1 Model structure of the partitioned survival model with the three health states. (A) Treatment strategies. (B) Partitioned survival model. P, partitioned survival model.

Liu L, *et al*. *BMJ Open* 2025;**15**:e094804. doi:10.1136/bmjopen-2024-094804

Table 1 Key model inputs

Parameter	Base case (Range)		Distribution	Source
	USA	China		
Costs input (US$)				
Atezolizumab per 1200 mg	9727.56 (7295.67 to 12 159.45)	4873.70 (3655.27 to 6092.12)	Gamma	24 25
Bevacizumab per 100 mg	713.54 (535.16 to 891.93)	222.88 (167.16 to 278.60)	Gamma	24 25
Sorafenib per 200 mg	210.83 (158.12 to 263.54)	14.12 (10.59 to 17.64)	Gamma	24 25
Cost of intravenous drug administration per unit	298 (223.50 to 372.50)	134.93 (101.20 to 168.66)	Gamma	12 29
Cost of scans per visit	783 (587.25 to 978.75)	85.01 (63.76 to 106.26)	Gamma	4 11
Cost of laboratory tests per month	285.64 (214.23 to 357.05)	57.83 (43.37 to 72.29)	Gamma	11 26
Cost of terminal care in end-of-life	7894.00 (5920.50 to 9867.50)	1460.30 (1095.23 to 1825.38)	Gamma	12 29
Utility value				
Utility in PFS	0.84 (0.63 to 1)	0.76 (0.57 to 0.95)	Beta	11 12
Utility in PD	0.71 (0.54 to 0.89)	0.68 (0.51 to 0.85)	Beta	11 12
AEs disutility				
Grade 1 and 2	0.014 (0.01 to 0.02)	0.09 (0.07 to 0.11)	Beta	12 58
Grade 3 and higher	0.157 (0.00 to 0.20)	0.20 (0.15 to 0.25)	Beta	12 58
Others				
Weight (kilogram)	71.4 (53.55 to 89.25)	65.00 (48.75 to 81.25)	Normal	12 23
Body surface area (m^2)	1.86 (1.40 to 2.23)	1.72 (1.38 to 2.06)	Normal	12
Discount rate (%)	3 (0 to 8)	5 (0 to 8)	Beta	31 32

AEs, adverse events; PD, progressed disease; PFS, progression-free survival.

Clinical data inputs

To estimate the proportion of three health states, the PFS and OS curves during the IMbrave150 trial period were derived by GetData Graph Digitizer, V.2.18.[17] The original and reconstructed Kaplan-Meier curves are shown in online supplemental figure 1. Given that the time horizon in our economic evaluation surpasses the follow-up period in the IMbrave150 trial,[13] we employed the following parametric survival functions to fit and extrapolate the OS and PFS curves: exponential, gamma, Weibull, log-normal, log-logistic, generalised gamma, Gompertz and Royston-Parmar spline.[18–20] The best-fitted survival functions were selected according to visual assessment, Akaike information criterion, Bayesian information criterion and oncologist's opinions.[18] Finally, the PFS distribution and the OS distribution were 1-knot Royston-Parmar and 2-knot Royston-Parmar distributions for atezolizumab plus bevacizumab, 2-knot Royston-Parmar and log-normal for sorafenib. The parameter values and goodness-of-fit of survival functions are shown in online supplemental table 1. The proportions of patients with PFS and OS were calculated by using the selected survival function. The subsequent treatment after disease progression and safety data are derived from the IMbrave150 trial, with all key clinical inputs presented in table 1 and online supplemental tables 2 and 3.

Cost and utility inputs

Only direct medical costs within the healthcare system were included in this study (table 1), including the costs for drug acquisition, drug administration, subsequent treatment after the disease progressed, laboratory tests, scans, end-of-life care and management of AEs. All cost inputs were reported as 2022 US dollars with Chinese yuan transformed to US dollars by the exchange rate in 2022: US$1 = ¥6.73. The costs that did not correspond to 2022 prices were inflated to 2022 using the consumer price index.[21 22] According to the IMbrave150 trial,[13] patients received either 1200 mg of atezolizumab plus 15 mg/kg of bevacizumab intravenously every 3 weeks, or 400 mg of sorafenib orally two times per day. More than half (56%) continued to receive treatment with atezolizumab and bevacizumab after disease progression.[13] The median number of treatment cycles received after the investigator-assessed disease progression was 5 (range, 1–33) for atezolizumab and 4 (range, 1–33) for bevacizumab.[13] To calculate the dosage of bevacizumab, we assumed that the weight was 71.4 kg in the USA and 65.0 kg in China for a typical patient.[12 23] The prices of atezolizumab, bevacizumab and sorafenib were collected from US Micromedex RED BOOK Online and Chinese bid-winning price.[24 25]

After disease progression, 36.0% of patients in the atezolizumab plus bevacizumab group and 52% in the sorafenib group received subsequent systemic medication therapy, and the proportion and cost for each subsequent therapy are shown in online supplemental table 2, which were estimated from the IMbrave150 trial, Chinese

bid-winning price and US Micromedex RED BOOK Online.[13 24 25] The costs for laboratory tests (US$285.64 in the USA, US$57.83 in China per month),[11 26] subsequent best supportive care (US$887.87, US$119.00 in China per cycle),[27 28] CT scan (US$783.00 in the USA, US$85.01 in China per visit)[4 11] and terminal care in end-of-life (US$7894.00 in the USA, US$1460.30 in China per patient)[12 29] were collected from published literature about patients with unresectable HCC. The analysis included the costs associated with the management of grade 3 or higher AEs (probability≥5%), which were extracted from the literature (online supplemental table 3).[13]

Each health state was assigned a health utility preference on a scale of 0 (death) to 1 (perfect health). Given that utility values were not reported in the IMbrave150 trial, we extrapolated them by leveraging the previously reported utility values with similar features in advanced HCC. The utility values of the PFS state associated with unresectable HCC were 0.84 in the USA and 0.76 in China.[11 12] The utility values of PD state were 0.71 in the USA and 0.67 in China, which were derived from patients with unresectable HCC.[11 12] The disutility values due to grade 1 or 2 and grade 3 or higher AEs were included in this analysis.[30] All AEs were assumed to have occurred during the first cycle.

Base-case analysis

Clinical and economic outcomes were compared between the atezolizumab plus bevacizumab group and sorafenib group, including average life-years, quality-adjusted life-years (QALYs), and costs per patient. Furthermore, the incremental cost-effectiveness ratio (ICER) was calculated as the incremental costs per additionally gained QALY between the two groups. When the ICER was lower than the prespecified willingness-to-pay threshold (WTP, US$150 000.00/QALY in the USA and three times gross domestic product per capita per QALY (US$38 201.19/QALY) in China), the atezolizumab plus bevacizumab strategy was considered cost-effective according to the recommendation of the Institute for Clinical and Economic Review's Reference Case for Economic Evaluations and Guidelines for Evaluation of Chinese Pharmacoeconomics.[31 32] Costs and effectiveness were discounted at an annual rate of 5% in China and 3% in the USA.[31 32] The incremental net health benefits (INHB) and incremental net monetary benefits (INMB) were also applied in our analyses by the following formulas: INHB (λ) = ($\mu_{E1} - \mu_{E0}$) − ($\mu_{C1} - \mu_{C0}$)/λ = $\Delta E - \Delta C/\lambda$; INMB ($\lambda$) = ($\mu_{E1} - \mu_{E0}$) × λ − ($\mu_{C1} - \mu_{C0}$) = $\Delta E \times \lambda - \Delta C$, where μ_{Ci} and μ_{Ei} were the costs and QALYs of atezolizumab plus bevacizumab (i=1) or sorafenib (i=0), respectively, and λ was the WTP threshold.[33 34]

Sensitivity, scenario and subgroup analyses

To assess the robustness of the base-case results, we performed both one-way and probabilistic sensitivity analyses (PSA). One-way sensitivity analyses were performed for all model parameters. The range of each parameter was determined based on either the reported 95% CI in the referenced studies or by assuming a 25% variation from the base-case value (table 1). In PSA, a Monte Carlo simulation with 1000 iterations was generated by simultaneously sampling the key model parameters from the predefined distributions. We used a gamma distribution for cost-related parameters and a beta distribution for proportion and health utility parameters. The results from these 1000 iterations were used to construct a cost-effectiveness acceptability curve, illustrating the probability of atezolizumab plus bevacizumab being considered cost-effective across different WTP thresholds for health gains (QALYs). With the PSA results, the expected value of perfect information (EVPI) was performed, which quantified the value of acquiring perfect information about all aspects of the decision, that is, eliminating all uncertainty.[35 36]

We then conducted a scenario analysis with respect to five conditions: a gradual 25% price reduction of atezolizumab (100% price to 25% of the price), a cost-threshold analysis (the price of atezolizumab that would make it cost-effective), different time horizons (5, 10, 20, 30 years), considering life-years as effectiveness and developing a Markov model to replace the partitioned survival model. Lastly, to investigate the uncertainty of economic outcomes caused by the subpopulations, exploratory subgroup analyses were performed for the prespecified subgroups that were reported in the IMbrave150 trial by varying the HRs for OS and PFS.[13] Survival curves were fitted with the flexsurv package in R, V.4.1.1, 2021,[37] and the economic evaluation model was developed in Microsoft Excel 2019.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Base-case analysis

Compared with the sorafenib strategy, atezolizumab plus bevacizumab provided an additional 0.57 QALYs in the USA and 0.47 QALYs in China for the patients with unresectable HCC, with an incremental cost of US$143 484.73 in the USA and US$85 460.80 in China (table 2). The ICERs for the atezolizumab plus bevacizumab versus the sorafenib were US$253 247.07/QALY in the USA and US$181 552.71/QALY in China. Moreover, the results of the base-case analysis without discounting are shown in online supplemental table 4.

Sensitivity analysis

The one-way sensitivity analyses revealed that the results of the model were most sensitive to the proportion of receiving tyrosine kinase inhibitor (TKI)-based subsequent treatment in the US perspective and the cost of

Table 2 Summary of cost and outcome results per patient in the base-case analysis

	USA		China	
Variables	Atezolizumab plus bevacizumab	Sorafenib	Atezolizumab plus bevacizumab	Sorafenib
Cost, US$				
Drug	291 417.32	173 520.81	115 279.34	11 469.53
Overall	620 759.73	477 275.00	162 093.52	76 632.73
Life-years, year				
Progression-free	0.97	0.57	0.94	0.56
Overall	2.52	1.8	2.35	1.71
QALYs, QALY	1.92	1.35	1.67	1.20
ICER, US$/QALY	253 247.07	NA	181 552.71	NA
INHB, QALY*	−0.39	NA	−1.90	NA
INMB, US$*	−58 497.73	NA	−68 469.49	NA
EVPI, US$	3658.41	NA	0.00	NA

*Calculated by the willingness-to-pay threshold, US$150 000.00/QALY in the USA, US$38 201.19/QALY in China.
EVPI, expected value of perfect information; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NA, not applicable; QALY, quality-adjusted life-years.

atezolizumab in the Chinese perspective (figure 2). Other considerable influential parameters were the cost of sorafenib and atezolizumab in the USA (figure 2A), and the utility of PFS and cost of bevacizumab in China (figure 2B). However, all the varying parameters did not result in the ICERs being below the prespecified threshold in the USA or China. The PSA showed that the mean ICER was US$256 531.14/QALY and US$181 998.30/QALY in the USA and China, respectively (figure 3A). The cost-effectiveness acceptability curve showed that the atezolizumab plus bevacizumab regimen was 13.60% and 0.00% of being cost-effective at prespecified threshold in the USA and in China, respectively (figure 3B). Both one-way sensitivity analysis and PSA are essential for testing the robustness of the results. One-way sensitivity analysis provides a focused assessment of the impact of changing one parameter on ICER at a time, while PSA provides a broader perspective on how uncertainty in multiple parameters affects the ICER at a time. In the context of our study, EVPI enhanced the robustness of the results by quantifying the impact of uncertainty on decision-making. The lower EVPI values (US$3658.41/patient and US$0/patient in the USA and China) indicate that the current level of uncertainty has little or no impact on cost-effectiveness decisions in the USA and China, respectively. Therefore, there is little or no return on investment for obtaining more information (table 2).

Scenario analysis

Considering the WTP threshold, the atezolizumab plus bevacizumab treatment would become cost-effective when the cost of atezolizumab decreased to 67.85% and 18.45% of its original price in the USA and China, respectively. When applying different time horizons to the model, the probabilities of atezolizumab plus bevacizumab being cost-effective were similar compared with the base-case analysis. If effectiveness was considered in life-years instead of QALYs, the probability that the atezolizumab plus bevacizumab was cost-effective would increase from 13.60% to 74.15% in the USA, but the probability remained 0.00% in China (online supplemental table 5). In addition, the results using the Markov model

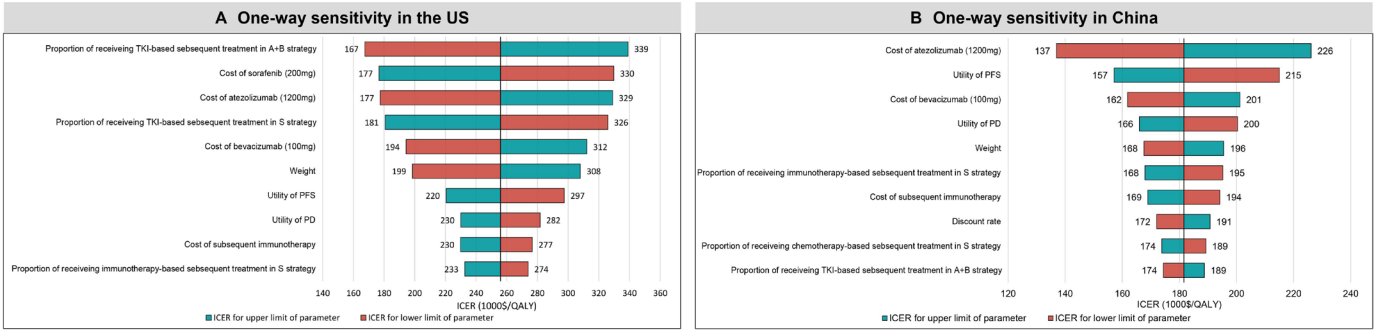

Figure 2 Tornado diagram of one-way sensitivity analyses of atezolizumab plus bevacizumab versus sorafenib in (A) USA (B) China. A, atezolizumab; B, bevacizumab; ICER, incremental cost-effectiveness ratio; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life-years; S, sorafenib; TKI, tyrosine kinase inhibitor.

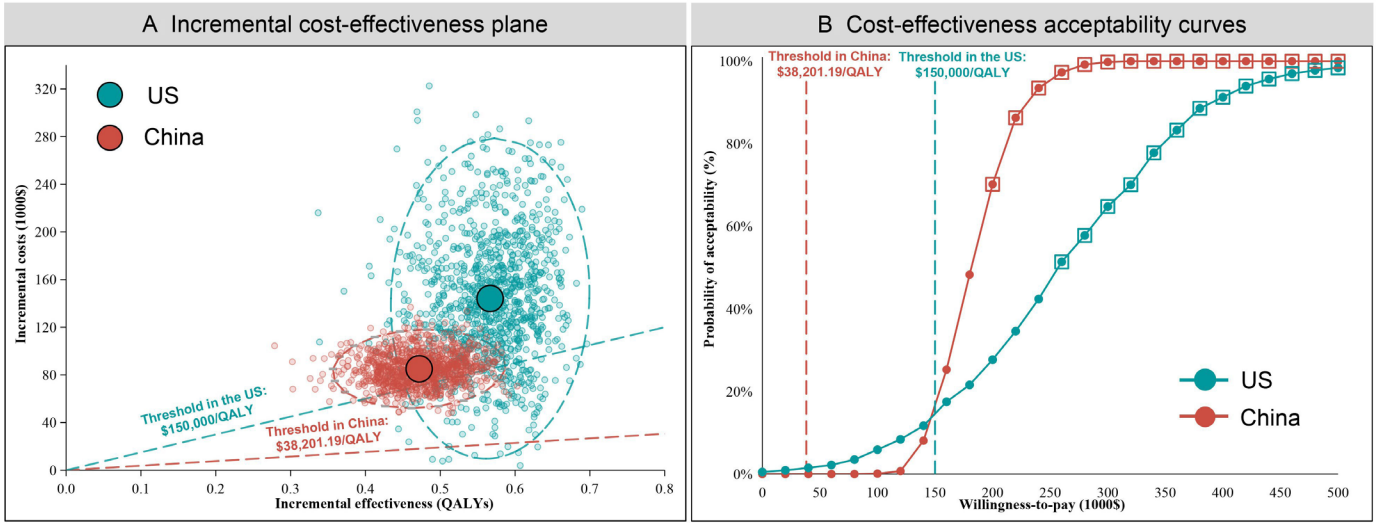

Figure 3 Probabilistic sensitivity analyses of atezolizumab plus bevacizumab versus sorafenib (A) Cost-effectiveness plane (B) Acceptability curves. QALY, quality-adjusted life-years.

were similar to those in the partitioned survival model. All scenarios achieved their maximum EVPI within the WTP threshold of US$300 000, and the maximum EVPI varied between US$10 267.18 and US$20 046.69 in the USA, and US$1850.59 and US$6332.31 in China (figure 4).

Subgroup analyses

The subgroup analyses, which were conducted by varying the HRs for OS and PFS simultaneously, revealed that atezolizumab plus bevacizumab was associated with negative INHBs in all subgroups in China (figure 5). In addition, atezolizumab plus bevacizumab was also associated with primarily negative INHBs among the most subgroups in the USA. The positive INHB with 0.23 (−0.63 to 0.75) for patients with non-viral aetiology represents the sole subgroup that exhibits economic viability.

DISCUSSION

The combination of atezolizumab plus bevacizumab as a first-line treatment for advanced HCC has demonstrated acceptable safety and promising efficacy, potentially emerging as the preferred therapeutic option for patients with advanced HCC, particularly when significant tumour control is required.[10 13 38] However, the significant escalation in medical resource consumption has inevitably garnered the attention of healthcare professionals and administrators due to the widespread use of these drugs. The study first investigated the economic assessment of atezolizumab plus bevacizumab compared with sorafenib as a first-line systemic treatment for unresectable HCC, based on the updated efficacy and safety data from IMbrave150, and our findings held significant implications for high-income and middle-income populations. The findings suggest that the combination therapy of atezolizumab and bevacizumab results in an additional 0.72 life-years/0.57 QALYs in the USA and 0.64 life-years/0.47 QALYs in China compared with standard sorafenib treatment, although with a significant increase in costs, yielding an average ICER of US$253 247.07/QALY in the USA and US$181 552.71/QALY in China. The primary finding demonstrated that the combination therapy of atezolizumab plus bevacizumab did not exhibit cost-effectiveness in either the USA or China, with threshold values of US$150 000 and US$36 096.29 per QALY respectively. The results of the probability sensitivity analysis indicate that atezolizumab plus bevacizumab demonstrates a 13.60% likelihood of cost-effectiveness in the USA, whereas this likelihood is negligible (0%) in China. In the one-way sensitivity analyses, within the range of fluctuations, neither adjusting any parameter could reverse the lack of economic advantage for atezolizumab plus bevacizumab. The cost of subsequent treatment is the most influential parameter in the USA, primarily due to regorafenib being priced 12 times higher than in China, and regorafenib serves as a crucial therapeutic drug in second-line treatment for advanced HCC according to international guidelines and clinical trials. Moreover, the results of scenario analyses such as various time horizons, life-year as effectiveness and Markov model showed similar economic outcomes.

Notably, in instances where the survival data from IMbrave150 were incomplete (ie, OS data were not yet mature), certain studies conducted pharmacoeconomic analyses by extrapolating from other comparable OS data, performing meta-analyses or using mixed methods approaches, etc, despite the potential introduction of significant bias into the findings.[11 12 39–42] The aforementioned studies have demonstrated that the atezolizumab plus bevacizumab treatment for unresectable HCC lacks cost-effectiveness in most countries and regions, highlighting reasonable pricing and yielding varying results in subgroup analyses. Su *et al*[12] demonstrated that atezolizumab plus bevacizumab treatment was cost-effective among patients in the USA across seven subgroups, with

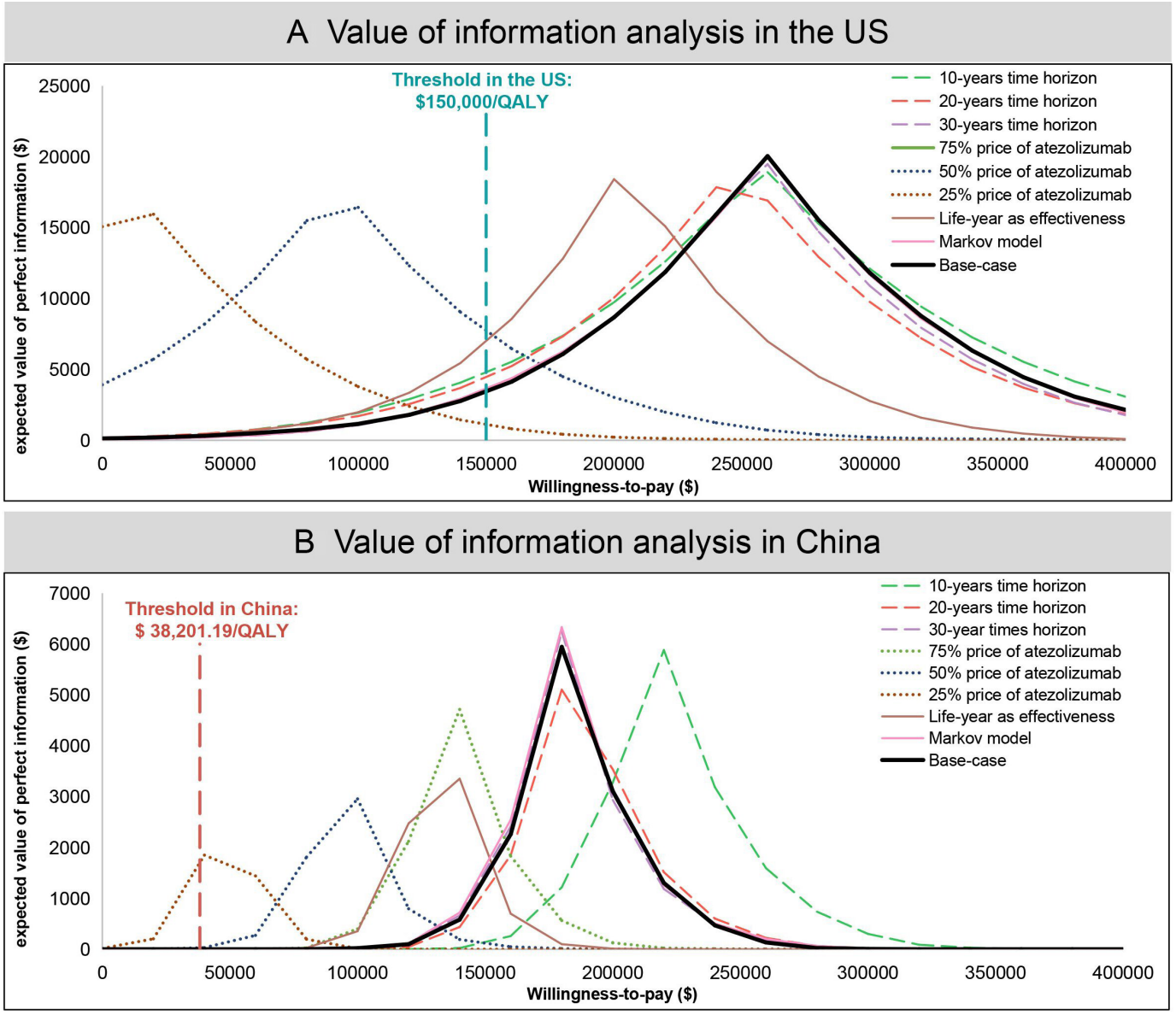

Figure 4 Value of information analysis results among different scenarios in (A) USA (B) China. QALY, quality-adjusted life-years.

variations only observed in the HRs for OS or PFS. In contrast, Zhang *et al*[11] did not identify any association between the treatment and cost-effectiveness within any subgroup, which aligns with our findings primarily due to our consideration of HRs for both PFS and OS. However, the sample size of each exploratory subgroup was limited, and the utilisation of HRs for calculating the survival benefit in the intervention group may introduce considerable uncertainty into the model, necessitating cautious interpretation and generalisation. Although Wen *et al*'s[39] research findings align with ours, indicating that the treatment of atezolizumab plus bevacizumab is not cost-effective in both the USA and China, our study provides updates and additional insights. In addition to incorporating validated survival data into the model, we also calculated the EVPI under different scenarios at the designated WTP, which represents the additional value gained by fully understanding all individual possibilities. According to the PSA analysis results, in China, the combination of atezolizumab and bevacizumab is entirely uneconomical (0%), suggesting that the value of acquiring perfect information for decision-making is 0. Conversely, in the USA, there is a 13.60% uncertainty associated with this regimen. Obtaining perfect information could add a value of US$3914.24 for decision-makers. Moreover, a systematic review[43] demonstrated that atezolizumab plus bevacizumab was not a cost-effective intervention in advanced HCC, regardless of the country and time horizon. Although atezolizumab plus bevacizumab can significantly improve the survival of patients with other cancer types, such as cervical cancer[44] and renal cell carcinoma,[45] studies[46–49] have shown that it is not cost-effective in these cancers either. Decision-makers should take into account the findings from economic evaluations and assessments of affordability prior to adopting new therapies.

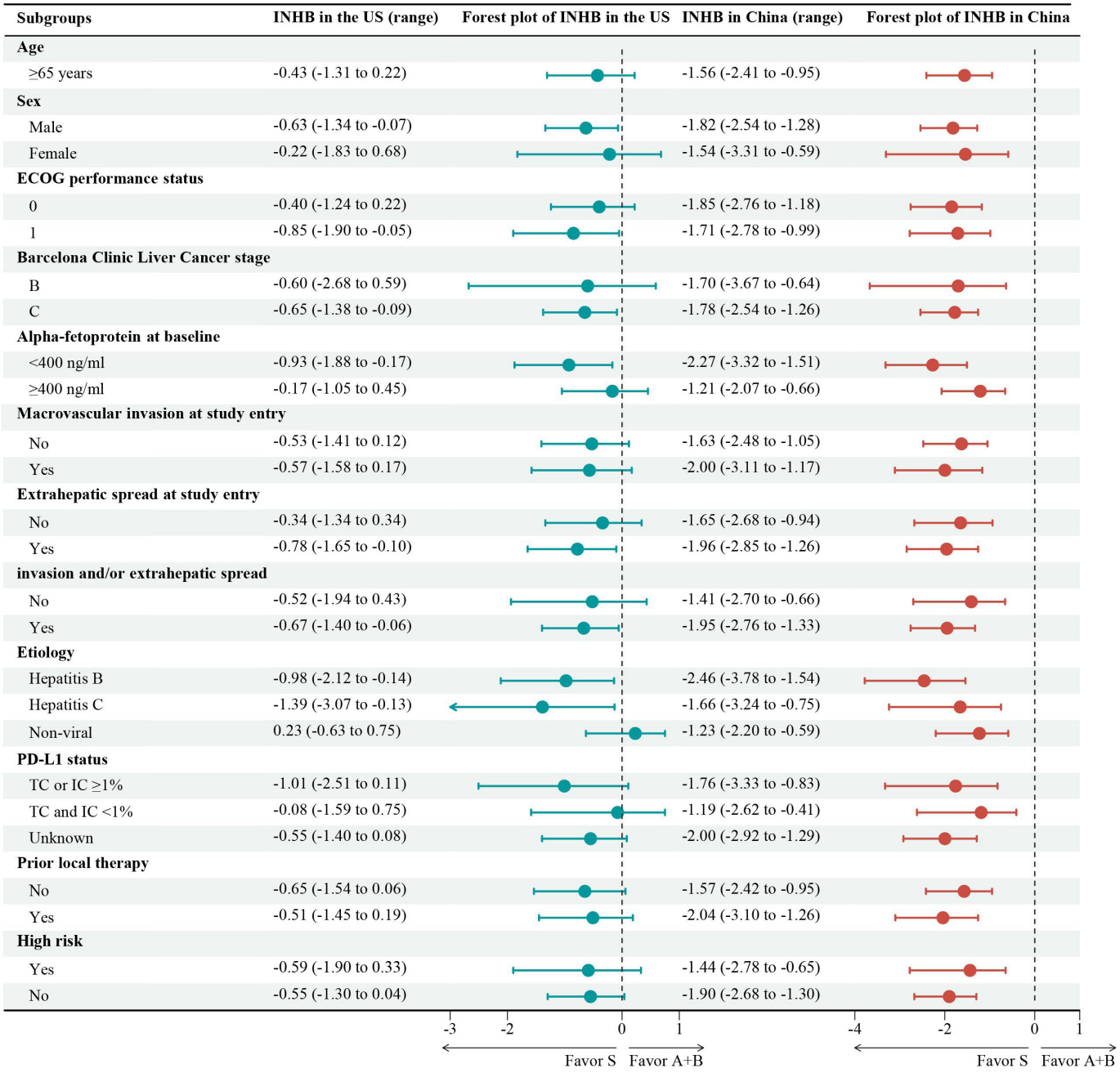

Figure 5 Subgroup analysis results in the USA and China. A, atezolizumab; B, bevacizumab; ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cell; INHB, incremental net health benefit; PD-L1, programmed cell death-ligand 1; S, sorafenib; TC, tumor cell.

The high expenses associated with research and development for novel pharmaceuticals have led to the generally elevated costs of ICIs, which are frequently not covered by national health insurance.[50] Consequently, this has resulted in a lack of cost-effectiveness in the treatment of various malignant tumours, even in high-income countries.[51] The incorporation of bevacizumab into atezolizumab leads to an augmented expenditure for the combined therapy. However, regulatory authorities and authoritative guidelines across different countries primarily approve and recommend the utilisation of new drugs based on their efficacy and safety, paying relatively less attention to drug pricing even when cost-effectiveness is lacking. The primary objective of conducting pharmacoeconomic evaluations is to provide comprehensive information on drug pricing, which plays a pivotal role in achieving a balance between patient affordability and the financial burden borne by the public healthcare system. According to our research findings, the total costs of first-line drugs (atezolizumab plus bevacizumab and sorafenib) in the USA amount to US$291 417.32 and US$173 520.81, respectively, whereas in China they stand at US$115 279.34 and US$11 469.53, respectively. A significant and distinct disparity exists between the USA and

China regarding long-term costs due to the comparatively lower prices of these aforementioned drugs in China compared with those in the USA. Moreover, the atezolizumab plus bevacizumab treatment becomes favourable when the cost of atezolizumab decreases to 67.85% and 18.45% of its original price in the USA and China, respectively. Due to the difference in WTP between China and the USA, even when life-years are adopted as the effect measurement indicator since the ICER decreases but is still much higher than the WTP in China, the economic probability of atezolizumab plus bevacizumab in China is still 0% (while in the USA, it increases from 13.60% to 74.15%). The absence of cost-effectiveness does not imply opposition to the utilisation of atezolizumab plus bevacizumab in patients with advanced HCC. Instead, it is recommended that decision-makers allocate more resources to interventions with higher cost-effectiveness and select these interventions in order of increasing ICERs, so as to maximise health benefits under limited resources.[52 53] The government can facilitate the development of generic drugs and biosimilars, as well as engage in effective negotiations or discussions with pharmaceutical companies (such as adopting a pricing model based on international benchmarks in the USA, or implementing volume-based procurement in China),[50 54 55] in order to mitigate the cost of atezolizumab plus bevacizumab and enhance its economic viability.

The analysis is subject to several limitations. First, by fitting the parameter distribution to the Kaplan-Meier PFS and OS data in IMbrave150, it is possible to estimate the health benefits beyond the follow-up period. However, in long-term follow-up of patients receiving immunotherapy, there may be a plateau phase in the tail of the survival curve.[56] The parameter model did not account for the possibility of long-term survival and might underestimate the effectiveness of immunotherapy. Second, the parameters of the model excessively rely on the findings of IMbrave150, which inadequately reflect the genuine clinical practice and resource utilisation in advanced HCC. For instance, patients enrolled in clinical trials generally exhibit a higher level of overall health compared with patients with typical late-stage HCC and demonstrate enhanced adherence to treatment protocols.[57] Moreover, surgical intervention also represents a viable alternative. Third, the customised therapeutic regimen for subsequent treatment in the IMbrave 150 trial remained unclear. We hypothesised regorafenib, pembrolizumab and bevacizumab as representative examples of TKIs, immunotherapy and angiogenesis inhibitors, respectively, to estimate the cost of second-line treatment. However, it should be noted that other drugs within these categories may also serve as potential options for second-line therapy. Fourth, the utility values were derived from previous studies on sorafenib for advanced HCC, rather than IMbrave150. The IMbrave150 trial demonstrated that atezolizumab plus bevacizumab significantly delayed the decline in quality of life, regardless of whether patients were in PFS or PD state. Therefore, using the same utility values in both groups might underestimate the effectiveness of atezolizumab plus bevacizumab. Precisely, this underestimation does not undermine the cost-effectiveness outcome, given that even without a reduction in utility following disease progression during the atezolizumab plus bevacizumab treatment, the ICER values of US$236 745.27/QALY in the USA and US$173 877.01/QALY in China still surpass the WTP thresholds. Finally, the model excluded the costs of grade 1 and grade 2 AEs, which may have led to an overestimation of the economic outcomes for atezolizumab plus bevacizumab. However, according to the results of the one-way sensitivity analysis, this limitation may not be a major factor as AE costs have a minimal impact on the model outputs.

CONCLUSIONS

The present economic evaluation suggested that atezolizumab plus bevacizumab is unlikely to be cost-effective compared with sorafenib for patients with unresectable HCC in the context of the USA and China. Significantly reducing the costs of atezolizumab and bevacizumab may yield favourable cost-effectiveness. We confidently assert that these research findings can be extensively applied to other regions, given that the USA and China, respectively, serve as prominent exemplars of developed and developing countries.

Author affiliations
[1]Department of Pharmacy, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[2]Department of Pharmacy, The Second Affiliated Hospital of Army Medical University, Chongqing, China
[3]Outpatient Department Office, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[4]Department of Pharmacy, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Contributors Conceptualisation, YS and QZ; Formal analysis, LL, YS and LW; Resources, LW, YD and QZ; Software, LL and YS; Supervision, QZ; Visualisation, LW and YD; Writing—review and editing, LL, LW, YS, YD and QZ. YS is responsible for the overall content as the guarantor. All authors read and approved the final manuscript.

Funding This study was supported by grants from the National Key Research and Development Program of China (No. 2023YFF1205000), the National Natural Science Foundation of China (No. 82104476), Talent Project established by Chinese Pharmaceutical Association Hospital Pharmacy Department (No. CPA-Z05-ZC-2023-003), Dawning Program of Wuhan Knowledge Innovation Special Project (No. 2023020201020501).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval 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 supplementary information.

ORCID iD

Qilin Zhang http://orcid.org/0000-0002-4779-3875

REFERENCES

1 Sung H, Ferlay J, Siegel RL, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA A Cancer J Clinicians* 2021;71:209–49.
2 Park J-W, Chen M, Colombo M, *et al*. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015;35:2155–66.
3 wang L, Peng Y, Qin S, *et al*. First-line systemic treatment strategies for unresectable hepatocellular carcinoma: A cost-effectiveness analysis. *PLoS ONE* 2023;18:e0279786.
4 Sun K-X, Cao S-S, Shi F-H, *et al*. First-line treatments for advanced hepatocellular carcinoma: a network meta-analysis and cost-effectiveness analysis in China and the United States. *Therap Adv Gastroenterol* 2022;15:17562848221140662.
5 Zhao M, Pan X, Yin Y, *et al*. Cost-Effectiveness Analysis of Five Systemic Treatments for Unresectable Hepatocellular Carcinoma in China: An Economic Evaluation Based on Network Meta-Analysis. *Front Public Health* 2022;10:869960.
6 Johnson PJ, Qin S, Park J-W, *et al*. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol* 2013;31:3517–24.
7 Kudo M, Finn RS, Qin S, *et al*. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391:1163–73.
8 Rizzo A, Cusmai A, Gadaleta-Caldarola G, *et al*. Which role for predictors of response to immune checkpoint inhibitors in hepatocellular carcinoma? *Expert Rev Gastroenterol Hepatol* 2022;16:333–9.
9 Cheng A-L, Hsu C, Chan SL, *et al*. Challenges of combination therapy with immune checkpoint inhibitors for hepatocellular carcinoma. *J Hepatol* 2020;72:307–19.
10 Finn RS, Qin S, Ikeda M, *et al*. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med* 2020;382:1894–905.
11 Zhang X, Wang J, Shi J, *et al*. Cost-effectiveness of Atezolizumab Plus Bevacizumab vs Sorafenib for Patients With Unresectable or Metastatic Hepatocellular Carcinoma. *JAMA Netw Open* 2021;4:e214846.
12 Su D, Wu B, Shi L. Cost-effectiveness of Atezolizumab Plus Bevacizumab vs Sorafenib as First-Line Treatment of Unresectable Hepatocellular Carcinoma. *JAMA Netw Open* 2021;4:e210037.
13 Cheng A-L, Qin S, Ikeda M, *et al*. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol* 2022;76:862–73.
14 National Comprehensive Cancer Network Guidelines. Hepatocellular Carcinoma (version 1, 2023), Available: https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf
15 Wang X, Li H, Zhang L, *et al*. Study on Guidelines of Chinese Society of Clinical Oncology (CSCO): Hepatocellular Carcinoma (2022). *Chinese J Bases Clin General Surg* 2023;30:403–7.
16 Husereau D, Drummond M, Augustovski F, *et al*. Consolidated Health Economic Evaluation Reporting Standards 2022. *Value Health* 2022;25:3–9.
17 Guyot P, Ades AE, Ouwens MJNM, *et al*. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;12:9.
18 Latimer NR. Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. *Med Decis Making* 2013;33:743–54.
19 Felizzi F, Paracha N, Pöhlmann J, *et al*. Mixture Cure Models in Oncology: A Tutorial and Practical Guidance. *Pharmacoecon Open* 2021;5:143–55.
20 Martinez EZ, Achcar JA, Jácome AAA, *et al*. Mixture and non-mixture cure fraction models based on the generalized modified Weibull distribution with an application to gastric cancer data. *Comput Methods Programs Biomed* 2013;112:343–55.
21 National Bureau of Statistics of China, 2021. Available: http://data.stats.gov.cn/english/index.htm
22 FRED Economic Data. Research: Federal Reserve Bank of St Louis. Consumer Price Index for all urban consumers: medical care in U.S, 2023. Available: https://fred.stlouisfed.org/series/CPIMEDSL
23 Zhang Q, Wu P, He X, *et al*. Cost-Effectiveness Analysis of Camrelizumab *vs*. Placebo Added to Chemotherapy as First-Line Therapy for Advanced or Metastatic Esophageal Squamous Cell Carcinoma in China. *Front Oncol* 2021;11:790373.
24 IBM Corporation. IBM Micromedex, Available: http://www.micromedexsolutions.com
25 Chinese Drug. Chinese Drug Price of Drug Centralized Bid Procurement, 2021. Available: https://db.yaozh.com/yaopinzhongbiao
26 Meng R, Zhang X, Zhou T, *et al*. Cost-effectiveness analysis of donafenib versus lenvatinib for first-line treatment of unresectable or metastatic hepatocellular carcinoma. *Expert Rev Pharmacoecon Outcomes Res* 2022;22:1079–86.
27 Li M, Lin S, Wilson L, *et al*. Cost-Effectiveness Analysis of Hepatic Arterial Infusion of FOLFOX Combined Sorafenib for Advanced Hepatocellular Carcinoma With Portal Vein Invasion. *Front Oncol* 2021;11:562135.
28 Soto-Perez-de-Celis E, Aguiar PN, Cordón ML, *et al*. Cost-Effectiveness of Cabozantinib in the Second-Line Treatment of Advanced Hepatocellular Carcinoma. *J Natl Compr Canc Netw* 2019;17:669–75.
29 Liu L, Wang L, Chen L, *et al*. Cost-effectiveness of sintilimab plus chemotherapy versus chemotherapy alone as first-line treatment of locally advanced or metastatic oesophageal squamous cell carcinoma. *Front Immunol* 2023;14:1092385.
30 Amdahl J, Diaz J, Park J, *et al*. Cost-effectiveness of pazopanib compared with sunitinib in metastatic renal cell carcinoma in Canada. *Curr Oncol* 2016;23:e340–54.
31 Yue X, Li Y, Wu J, *et al*. Current Development and Practice of Pharmacoeconomic Evaluation Guidelines for Universal Health Coverage in China. *Value Health Reg Issues* 2021;24:1–5.
32 Institute for Clinical and Economic Review. ICER's reference case for economic evaluations: principles and rationale, 2020. Available: https://icer.org/wp-content/uploads/2020/10/ICER_Reference_Case_013120.pdf
33 Craig BA, Black MA. Incremental cost-effectiveness ratio and incremental net-health benefit: two sides of the same coin. *Expert Rev Pharmacoecon Outcomes Res* 2001;1:37–46.
34 Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998;18:S68–80.
35 Fenwick E, Steuten L, Knies S, *et al*. Value of Information Analysis for Research Decisions-An Introduction: Report 1 of the ISPOR Value of Information Analysis Emerging Good Practices Task Force. *Value Health* 2020;23:139–50.
36 Rothery C, Strong M, Koffijberg HE, *et al*. Value of Information Analytical Methods: Report 2 of the ISPOR Value of Information Analysis Emerging Good Practices Task Force. *Value Health* 2020;23:277–86.
37 Jackson CH. flexsurv: A Platform for Parametric Survival Modeling in R. *J Stat Softw* 2016;70:i08.
38 Galle PR, Finn RS, Qin S, *et al*. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2021;22:991–1001.
39 Wen F, Zheng HR, Zhang PF, *et al*. Atezolizumab and bevacizumab combination compared with sorafenib as the first-line systemic treatment for patients with unresectable hepatocellular carcinoma: A cost-effectiveness analysis in China and the United states. *Liver Int* 2021;41:1097–104.
40 Chiang C-L, Chan S-K, Lee S-F, *et al*. First-Line Atezolizumab Plus Bevacizumab versus Sorafenib in Hepatocellular Carcinoma: A Cost-Effectiveness Analysis. *Cancers (Basel)* 2021;13:931.
41 Gaugain L, Cawston H, Dubois de Gennes C, *et al*. Cost-utility analysis of atezolizumab with bevacizumab in untreated unresectable or advanced hepatocellular carcinoma in France. *PLoS One* 2023;18:e0280442.

42 Hou YL, Wu B. Atezolizumab plus bevacizumab versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma: a cost-effectiveness analysis. *Cancer Commun* 2020;40:743–5.
43 Gong H, Ong SC, Li F, *et al*. Cost-effectiveness of immune checkpoint inhibitors as a first-line therapy for advanced hepatocellular carcinoma: a systematic review. *Health Econ Rev* 2024;14:48.
44 Oaknin A, Gladieff L, Martínez-García J, *et al*. Atezolizumab plus bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer (BEATcc): a randomised, open-label, phase 3 trial. *Lancet* 2024;403:31–43.
45 Motzer RJ, Powles T, Atkins MB, *et al*. Final Overall Survival and Molecular Analysis in IMmotion151, a Phase 3 Trial Comparing Atezolizumab Plus Bevacizumab vs Sunitinib in Patients With Previously Untreated Metastatic Renal Cell Carcinoma. *JAMA Oncol* 2022;8:275–80.
46 Lei J, Zhang J, You C, *et al*. First-Line Treatment With Atezolizumab Plus Bevacizumab and Chemotherapy for US Patients With Metastatic, Persistent, or Recurrent Cervical Cancer: A Cost-Effectiveness Analysis. *Value Health* 2024;27:1528–34.
47 Wang S, Xie O, Wu M, *et al*. Cost-effectiveness of atezolizumab plus bevacizumab as first-line therapy for metastatic renal cell carcinoma. *Expert Rev Pharmacoecon Outcomes Res* 2025;25:173–8.
48 Cai H, Fang L, Lin J, *et al*. Atezolizumab plus bevacizumab and chemotherapy versus bevacizumab plus chemotherapy for metastatic cervical cancer: a cost-effectiveness analysis. *Front Pharmacol* 2024;15:1476256.
49 Lin Y, Li C, Wang C, *et al*. Atezolizumab plus bevacizumab and chemotherapy as first-line therapy for cervical cancer: a cost-effectiveness analysis in the US. *Front Immunol* 2024;15:1481584.
50 Rosamond T. The High Cost of Cancer Drugs and What We Can Do About It. *Mayo Clin Proc* 2013;88:306.
51 Verma V, Sprave T, Haque W, *et al*. A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors. *J Immunother Cancer* 2018;6:128.
52 Cadier B, Bulsei J, Nahon P, *et al*. Early detection and curative treatment of hepatocellular carcinoma: A cost-effectiveness analysis in France and in the United States. *Hepatology* 2017;65:1237–48.
53 Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med* 2014;371:796–7.
54 Dyer O. US drug prices should be tied to foreign prices to tackle "global freeloading," says Trump. *BMJ* 2018;k4542.
55 Zhu Z, Wang Q, Sun Q, *et al*. Improving access to medicines and beyond: the national volume-based procurement policy in China. *BMJ Glob Health* 2023;8:e011535.
56 Allemani C, Matsuda T, Di Carlo V, *et al*. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018;391:1023–75.
57 Flather M, Delahunty N, Collinson J. Generalizing results of randomized trials to clinical practice: reliability and cautions. *Clin Trials* 2006;3:508–12.
58 Wu B, Zhang Q, Sun J. Cost-effectiveness of nivolumab plus ipilimumab as first-line therapy in advanced renal-cell carcinoma. *J Immunother Cancer* 2018;6:124.