Evaluating the cost-effectiveness of atezolizumab-bevacizumab in advanced hepatocellular carcinoma: Insights from Taiwan

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Abstract

Following the observed significant improvements in overall survival and progression-free survival in clinical trials, the combination of atezolizumab and bevacizumab has been recommended as a first-line therapy for patients with unresectable hepatocellular carcinoma. Despite its clinical benefits, the high cost associated with this treatment poses a substantial challenge in routine practice in Taiwan. This study aims to assess the cost-effectiveness of atezolizumab plus bevacizumab in comparison to sorafenib monotherapy. This study utilized partitioned survival analysis and extrapolated survival over a 20-year horizon to conduct a cost-effectiveness analysis from the perspective of the National Health Insurance Administration. Efficacy and utility data were directly extracted from the IMbrave150 trial, with input parameters adjusted to align with clinical practice in Taiwan. One-way deterministic and probabilistic sensitivity analyses were performed to assess the robustness of the results. Additionally, a scenario analysis was conducted to evaluate the impact of bevacizumab use on the outcomes. Compared to sorafenib, the combination of atezolizumab and bevacizumab resulted in an increase of 0.53 quality-adjusted life years (QALYs) and had an incremental cost of NT$1,867,151. The incremental cost-effectiveness ratio (ICER) was NT$3,523,768 per QALY, exceeding the commonly accepted willingness-to-pay threshold at NT$2,788,290 (three times Taiwan's gross domestic product per capita). One-way sensitivity analysis indicated that reducing the cost of atezolizumab plus bevacizumab to 70% would yield an ICER of NT$1,793,703. Scenario analysis demonstrated cost reduction in bevacizumab, either through the adoption of a biosimilar product or lower dosage, would make the combination cost-effective. Under Taiwan's National Health Insurance (NHI) system and based on the cost-effectiveness analysis in 2021, the combination of atezolizumab and bevacizumab is not cost-effective compared to sorafenib monotherapy for the treatment of unresectable hepatocellular carcinoma.

Keywords: Atezolizumab, Bevacizumab, Cost-effectiveness, Hepatocellular carcinoma

1. Background

Hepatocellular carcinoma (HCC) is a primary tumor of the liver and intrahepatic ducts. According to the World Health Organization, the global incidence of HCC in 2020 was 11.6 per 100,000 individuals, making it the seventh most common cancer. HCC also ranked as the fourth leading cause of cancer-related deaths worldwide, with a mortality rate of 10.7 per 100,000 individuals [1]. In Taiwan,

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the incidence and mortality rates of HCC are notably higher than the global averages. According to the 2018 cancer registration report, the incidence of HCC was 48.08 per 100,000 individuals, with a mortality rate of 34.86 per 100,000 individuals, making it the second leading cause of cancer-related death [2].

The treatment of HCC is guided by the Barcelona Clinic Liver Cancer staging system. For patients with unresectable advanced HCC, first-line treatment involves targeted therapies, such as sorafenib and lenvatinib [3–5]. Following the introduction of immune checkpoint inhibitors, nivolumab was approved as a second-line treatment for patients who do not respond to sorafenib [6]. The IMbrave150 trial demonstrated that the combination of atezolizumab and bevacizumab resulted in longer overall survival compared to sorafenib in patients with advanced HCC who had not received systemic therapy previously [7]. As a result, the National Comprehensive Cancer Network (NCCN) guidelines recommend atezolizumab plus bevacizumab as the preferred first-line systemic therapy for advanced HCC. Additionally, tremelimumab plus durvalumab has also been included as a preferred first-line treatment option in the latest NCCN guidelines [8].

Studies conducted in United States, Hong Kong, and China, have shown that the combination of atezolizumab and bevacizumab for advanced HCC is not cost-effective [9–11]. In Taiwan, approximately 99% of citizens are covered by the National Health Insurance (NHI) program. As part of this program, sorafenib and lenvatinib are approved as first-line systemic treatments for HCC whereas atezolizumab and bevacizumab are not. Since the combination of atezolizumab and bevacizumab was not reimbursed under NHI regulations in 2021, submitting local pharmacoeconomic data was crucial in facilitating its approval by the NHI administration [12]. Given the lack of local cost-effectiveness data for this treatment in advanced HCC, the present study aimed to address this gap.

2. Method

This cost-effectiveness analysis was conducted from the perspective of the NHI. Patients with advanced HCC receiving either atezolizumab and bevacizumab combination therapy or sorafenib monotherapy were recruited. Data on overall survival, progression-free survival, and adverse events were obtained from the IMbrave150 study [7].

A partition survival model was used to evaluate the transition probability. Data were analyzed using TreeAge Pro software (version 2021). Health state was classified as progression-free, disease progression, or death. We reconstructed the Kaplan–Meier curve from the IMbrave150 trial by using DigitizeIt software to calculate the transition probability for each health state. We used maximum likelihood estimation to estimate the survival probability coefficient and extrapolated the survival curve to a 20-year time horizon. We then applied the Akaike information criterion (AIC), Bayesian information criterion (BIC), and visual inspection to determine the optimal distribution (Supplementary Appendix 1). To ensure the robustness of our extrapolation, we evaluated multiple parametric survival models and calculated AIC and BIC values to assess their goodness-of-fit. The model with the lowest AIC and BIC values, along with superior visual alignment with observed data, was selected as the final extrapolation distribution.

We retrieved the utility data from IMbrave150 study [13]. To account for the impact of adverse events on quality of life measurements during the treatment period, we selected the utility from pre- and post-progression approach and grade 3 or higher adverse events. We then measured treatment effectiveness by using quality-adjusted life years (QALYs).

Direct costs included those associated with medication, management of adverse events, and end-of-life care. Medication cost was calculated based on the data from the IMbrave150 study. Atezolizumab and bevacizumab were administered at doses of 1200 and 15 mg/kg every 3 weeks until disease progression. Sorafenib was administered at a dose of 400 mg twice daily. Body weight was assumed to be 69.4 kg in accordance with data from a nutrition and health survey in Taiwan [14]. In the progression-free state, costs were calculated the per cycle until disease progression. For patients in the disease progression state, we assumed all of them received regorafenib, which was reimbursed by the NHI as a second-line therapy for advanced HCC. Non-medication costs included those related to disease management [15], intravenous administration, cytotoxic drug administration, and PD-L1 immunohistochemistry. We adopted the prices announced by the NHI administration in 2021. The costs of managing adverse events were also calculated, focusing on events with an incidence rates greater than 10% and those classified as severe.

We evaluated cost-effectiveness by calculating incremental cost-effectiveness ratios (ICERs) applying

a discount rate of 3% [16]. The willingness-to-pay threshold was set at NT$2,788,290, which was three times the annual gross domestic product per capita in Taiwan in 2021 [17].

We conducted both one-way deterministic and probabilistic sensitivity analyses. In the one-way deterministic sensitivity analysis, the discount rate was varied between 0% and 5%, utility values were adjusted between the lower 95% confidence interval (CI) to upper 95% CI, and medication cost were varied by ±30%. Variations in other costs were as follows: non-medication cost ranged from the first to third quartile, infusion and pharmacy service fee were set to zero, and end-of-life cost were set for 0–3 months. We used a Tornado diagram to visualize the impact of each variable. In the probabilistic sensitivity analysis, we applied 10,000 iterations of Monte Carlo simulations to estimate the distribution of effectiveness and cost. The base-case utility values were directly extracted from the IMbrave150 study. However, for the probabilistic sensitivity analysis, we applied a Beta probability distribution to these utility values to model parameter uncertainty. This statistical approach was adopted by previously published cost-effectiveness analyses of atezolizumab and bevacizumab [11]. The purpose of adopting the Beta distribution was to account for variability in the utility estimates while preserving the integrity of the IMbrave150 data. Similarly, for cost parameters, a Uniform probability distribution was applied to reflect plausible variations in economic inputs.

Finally, we conducted a scenario analysis to evaluate the impact of bevacizumab use. Because biosimilar bevacizumab is available in Taiwan, we assessed its potential effect on cost-effectiveness. Additionally, we examined the impact of modifying the bevacizumab dosage.

3. Result

The parameters used in the cost-effectiveness analysis are presented in Table 1. With a 3% discount rate and a 20-year extrapolation, total costs for the atezolizumab–bevacizumab group and sorafenib group were NT$4,726,423 and NT$2,859,271, respectively, resulting in an incremental cost of NT$1,867,151. The total QALYs in the atezolizumab–bevacizumab group were 1.728, which was 0.53 higher than in the sorafenib group. Comparing cost and QALYs, the ICER was NT$3,523,768 per QALY (Table 2). When considering willingness-to-pay threshold of three times gross domestic product, the combination therapy was not considered cost-effective (Fig. 1).

The results of one-way sensitivity analysis are presented in Table 3 and Fig. 2. The variable with the greatest impact was the cost of the atezolizumab

Table 2. Base case analysis.

Outcome	Atezolizumab plus bevacizumab		Sorafenib
Base case (20-year time horizon)			
Cost	NT$4,726,423		NT$2,859,271
QALYs	1.728		1.198
ICER		NT$3,523,768	
Base case (15-year time horizon)			
Cost	NT$4,722,206		NT$2,859,868
QALYs	1.725		1.198
ICER		NT$3,533,342	

ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life-years.

Table 1. Parameters for cost-effectiveness model.

	Atezolizumab plus bevacizumab	Sorafenib	Distribution	Source
Extrapolation simulation				
Overall survival	Log-normal	Log-normal		
Progression-free survival	Log-normal	Log-normal		
Utility				
Progression-free	0.74 (0.728, 0.764)	0.72 (0.695, 0.744)	Beta	NICE [ID1655]
Disease progression	0.72 (0.70, 0.735)	0.72 (0.70, 0.735)	Beta	NICE [ID1655]
Cost[a](NT$)				
Treatment	3,546,560	1,159,872	Uniform	NHIA
Management in progression-free state	97,080	97,080	Uniform	NHIA
Management in disease progression state	97,080	97,080	Uniform	NHIA
Cost of infusion	19,744	0		NHIA
Cost of pharmacy service for cytotoxic drug	5840	0		NHIA
Cost of end-of-life treatment	65,473	65,473	Uniform	NHIA
Cost of adverse events	469	192		NHIA

NHIA, National Health Insurance Administration.

[a] All costs were tested for sensitivity, and the variation range was ±30%; Cost of end-of-life treatment was tested for sensitivity, and the variation range was 0–3 months.

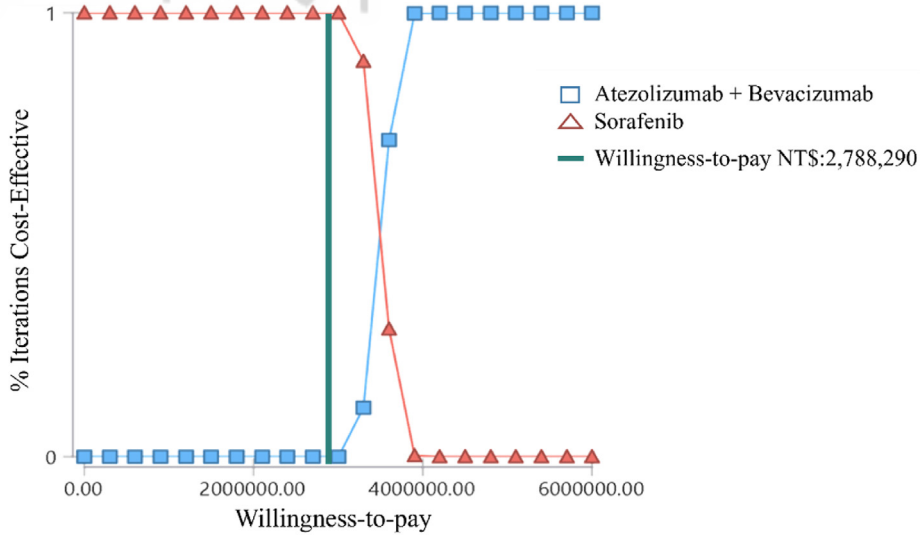

Fig. 1. Cost-effectiveness acceptability curve of atezolizumab plus bevacizumab versus sorafenib in advanced hepatocellular carcinoma.

and bevacizumab combination therapy, followed by the cost of sorafenib and the discount rate. When reducing the cost of atezolizumab with bevacizumab to 70%, the ICER decreased to NT$1,793,703, indicating that the treatment would be considered cost-effective.

The results of the probabilistic sensitivity analysis are illustrated in Fig. 3. Atezolizumab and bevacizumab combination therapy resulted in higher utility with a greater cost. All ICERs were above the willingness-to-pay threshold at three times the gross domestic product.

In the scenario analysis, we examined the impact of applying biosimilar bevacizumab and of adjusting the bevacizumab dose. When applying biosimilar bevacizumab and when reducing the dose to 7.5 mg/kg or less, the combination regimen was cost-effective (Fig. 4).

Table 3. One-way sensitivity analysis.

Sensitivity component	Baseline	Sensitivity analysis	ICER (NT$)	Distribution
Discount rate	3%	0%–5%	3,262,680–3,698,889	–
Utility				
PFS (atezolizumab + bevacizumab)	0.74	0.728 (lower 95% CI)–0.764 (upper 95% CI)	3,593,894–3,391,417	Beta
PFS (sorafenib)	0.72	0.695 (lower 95% CI)–0.744 (upper 95% CI)	3,437,226–3,611,049	Beta
DP	0.72	0.70 (lower 95% CI)–0.735 (upper 95% CI)	3,575,599–3,485,870	Beta
Cost				
Atezolizumab + bevacizumab	3,546,560	±30%	1,793,703–5,253,832	Uniform
Sorafenib	1,159,872	±30%	3,874,204–3,173,332	Uniform
Second-line treatment	892,080	±30%	3,329,798–3,717,737	–
Management in progression-free state	97,080	21,250 (median Q1)–120,390 (median Q3)	3,476,834–3,538,195	Uniform
Management in disease progression state	97,080	21,250 (median Q1)–120,390 (median Q3)	3,468,808–3,540,663	Uniform
Infusion	19,744	0	3,491,663	–
Cost of pharmacy service for cytotoxic drug	5840	0	3,514,272	–
End-of-life treatment	65,473	0 (0 months)–196,419 (Three months)	3,526,211–3,518,882	Uniform
Management for adverse events related to atezolizumab + bevacizumab	469	±30%	3,523,512–3,524,024	–
Management for adverse events related to sorafenib	192	±30%	3,523,873–3,523,662	–

CI: confidence interval; ICER: incremental cost-effectiveness ratio; DP: disease progression; PFS: progression-free survival; Q1: first quartile; Q3: third quartile.

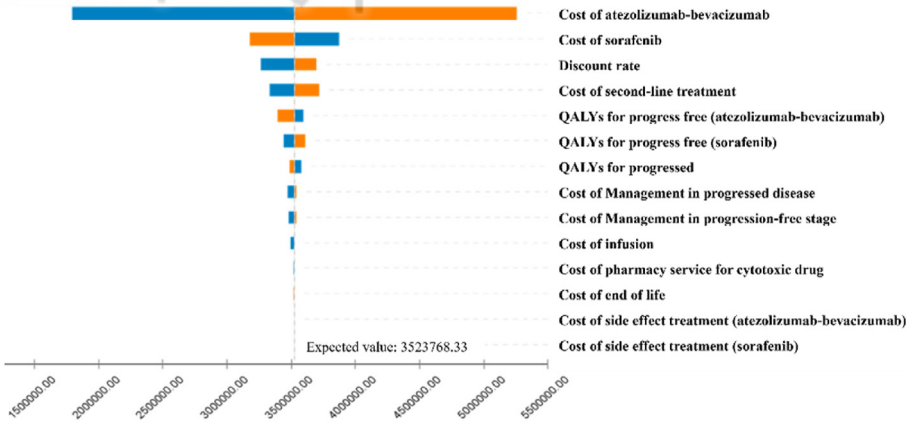

Fig. 2. Tornado diagram of one-way sensitivity analysis of atezolizumab plus bevacizumab versus sorafenib in advanced hepatocellular carcinoma; QALYs: Quality-adjusted life years.

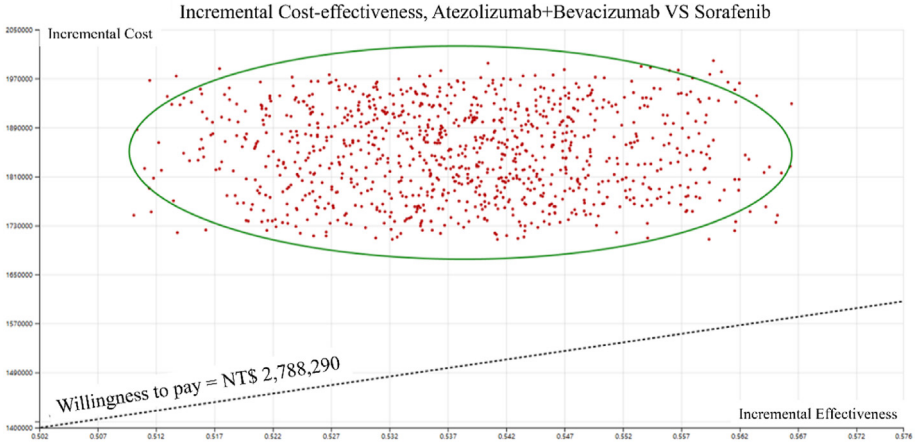

Fig. 3. Probabilistic sensitivity analysis of atezolizumab plus bevacizumab versus sorafenib in advanced hepatocellular carcinoma. Red dot indicates incremental cost for each probabilistic sensitivity analysis.

4. Discussion

This study compared the cost-effectiveness of atezolizumab–bevacizumab with that of sorafenib for the treatment of advanced HCC. In the base case analysis, the calculated ICER for atezolizumab–bevacizumab was NT$3,523,768 per QALY. Considering the willingness-to-pay threshold, the combination therapy was not deemed cost-effective.

Four other studies also found that atezolizumab–bevacizumab was not cost-effective (Supplementary Appendix 2) [9–11]. These studies exhibited differences in their designs. First, while the QALY was consistently 0.53, Chiang et al. reported a lower QALY value of 0.439 due to the adoption of a 5-year time horizon, which may not adequately capture the extended benefits of immunotherapy. In our study, we implemented a 20-year time horizon, allowing for a more comprehensive utility assessment. We also evaluated the effect of varying the extrapolated time horizon. Using a time horizon of 15 years resulted in a slight decrease in QALY value (to 0.527), but the ICER did not substantially change from its previous value (NT$3,533,342). Second, Chiang et al. and Feng et al. did not calculate the costs associated with second-line treatment, while Dan et al. excluded the costs related to the management of adverse events. In contrast, our study encompassed costs from both second-line therapy and management of adverse events, thereby reducing the likelihood of underestimating total expenditure.

This study employed a 20-year extrapolation of health state distribution based on survival curves. The AIC and BIC for the PFS curve indicated that the best fit was a generalized gamma distribution (Supplementary Appendix 1). However, given that

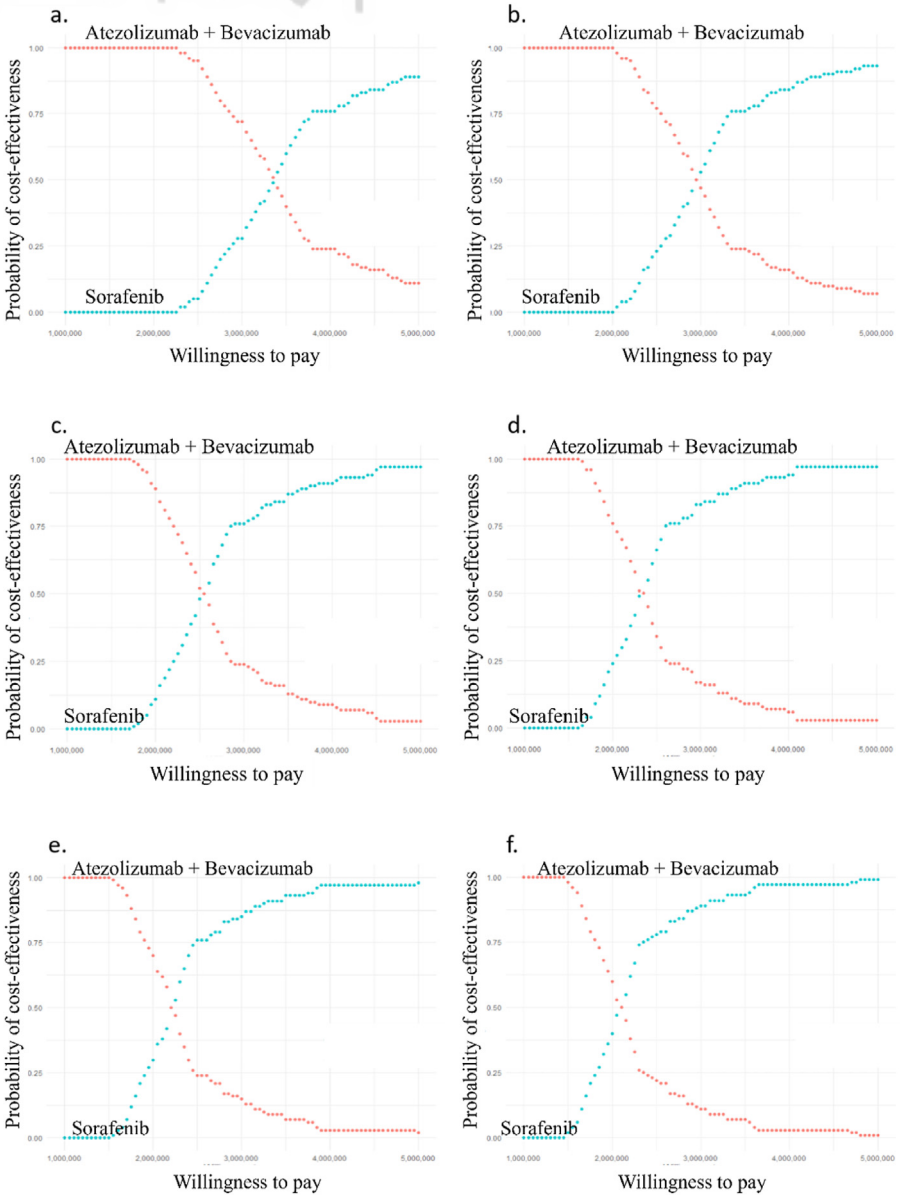

Fig. 4. Scenario analysis to test different dosage or brand of bevacizumab. a) Standard drug, 15 mg/kg; b) biosimilar drug, 15 mg/kg; c) standard drug, 7.5 mg/kg; d) biosimilar drug, 7.5 mg/kg; e) standard drug, 5 mg/kg; f) biosimilar drug, 5 mg/kg.

the generalized gamma distribution slightly overestimates survival rates in later periods, a log-normal distribution was adopted for the base case analysis. To examine the impact of the two distributions on the study outcomes, we compared the results obtained from each. Under the generalized gamma distribution, the QALY and incremental QALY values for the two groups were identical. The ICER under the generalized gamma distribution was NT$3,519,583, while under the log-normal distribution, it was NT$3,523,768. Although a slight difference was observed in the ICER values between the two distributions, this variation did not affect the overall results.

In our scenario analysis, the use of biosimilar bevacizumab or a reduced dosage of bevacizumab yielded a cost-effective outcome. Biosimilar bevacizumab is available in the Taiwanese market, with a cost per 100 mg vial that is NT$3000 lower than that of the original product. Clinical studies have demonstrated that the efficacy of biosimilar bevacizumab was noninferior to that of the original product in cancer treatment [18,19]. Regulatory authorities have employed indication extrapolation as a method for the approval of biosimilar products [20]. Therefore, the incorporation of biosimilar bevacizumab into this combination presents significant potential and is a rational choice. Regarding

dosage, studies have indicated that both high (15 mg/kg) and low (7.5 mg/kg) doses of bevacizumab exhibit similar efficacy in ovarian and lung cancers [21–24]. Additionally, the study by Sakai et al. provides real-world evidence supporting the feasibility of bevacizumab dose reduction specifically in HCC, demonstrating that a lower dose can maintain efficacy while potentially improving treatment adherence and safety [25]. Therefore, we considered the possibility of using a lower dosage of bevacizumab in this combination. Further research is necessary to validate these findings.

Our study was conducted in 2021, using cost data from 2021, at a time when the atezolizumab–bevacizumab combination therapy for advanced HCC was not reimbursed by NHI. However, as of August 2023, the combination has been approved for reimbursement under the NHI system with the price reduced to 65% of its 2021 value. Our sensitivity analysis indicated that the therapy would be cost-effective if the price were reduced to 70% or less. Consequently, the prices of atezolizumab and original bevacizumab were reduced from NT$132,450 to NT$83,258 and NT$8921 to NT$8324 in 2023, which equates to approximately 65% of the original cost, renders the combination therapy cost-effective according to our model.

Our study has several limitations. First, we reconstructed the survival curve and extrapolated it to 20 years. Extrapolation may overestimate the treatment efficacy of atezolizumab–bevacizumab. However, clinical trials have shown that immune checkpoint inhibitors induce a durable response and produce a long tail effect [26]. The combination of atezolizumab and bevacizumab has an additive effect and reprograms the microenvironment [7,27]. Updated data from the IMbrave150 trial also demonstrated an 18-month survival rate of 52% after a median follow-up of 15.6 months [7]. Our findings remained consistent when we employed a 15-year extrapolation, validating the robustness of the results. Second, regarding medical cost data, we computed expenditure within 3 years after the diagnosis of HCC, which may not fully correspond to the population in our study. This may have led to an underestimation of total cost. However, because our result indicated that the combination therapy was not cost-effective, this underestimation can be disregarded. Third, anticancer drug doses are often reduced to minimize the risk of adverse events. In the IMbrave150 study, the median doses of atezolizumab, bevacizumab, and sorafenib were 96%–98% of the standard doses [28]. Although we did not extensively analyze the impact of dose reductions on costs, the infrequency of dose reductions suggests that any effect would be negligible. Lastly, our study follows the IMbrave150 trial population, which includes patients with unresectable HCC, some of whom may belong to BCLC stage B. However, as the trial did not provide separate PFS and OS data for this subgroup, we were unable to conduct a specific cost-effectiveness analysis for BCLC stage B patients. Future research incorporating real-world data may help clarify the cost-effectiveness of atezolizumab–bevacizumab in this population.

In conclusion, this pharmacoeconomic analysis indicated that atezolizumab–bevacizumab is not a cost-effective treatment for advanced HCC in Taiwan. However, applying biosimilar bevacizumab or reducing the combination cost may improve its cost-effectiveness.

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Conflict of interest

The authors have no conflict of interest with any companies/organizations.

Supplementary

Appendix 1.

Table 1. AIC and BIC values for modeling overall survival.

Overall Survival	Atezolizumab + Bevacizumab		Sorafenib	
Model	AIC	BIC	AIC	BIC
Weibull (PH)	1495.43	1510.7	761.93	771.25
Weibull (AFT)	1495.46	1510.73	761.92	771.24
Log-normal	1486.3	1501.57	755.63	764.95
Log-logistic	1491.07	1506.34	757.92	767.24
Gen. Gamma	1488.91	1507.99	757.6	770.02
Gen. F	1494.52	1517.43	760.52	776.05
Gamma	1493.31	1508.57	760.77	770.09
Exponential	1507.5	1518.95	762.77	768.98

AIC: Akaike information criterion; BIC: Bayesian information criterion.

Table 2. AIC and BIC values for modeling progression-free survival.

Progression-Free Survival	Atezolizumab + Bevacizumab		Sorafenib	
Model	AIC	BIC	AIC	BIC
Weibull (PH)	1324.73	1339.99	614.65	623.96
Weibull (AFT)	1324.39	1339.66	614.65	623.97
Log-normal	1303.07	1318.34	602.72	612.04
Log-logistic	1312.27	1327.54	607.17	616.49
Gen. Gamma	1298.79	1317.87	604.54	616.97
Gen. F	1304.04	1326.94	607.36	622.89
Gamma	1321.63	1336.89	610.63	619.95
Exponential	1328.63	1340.08	627.42	633.63

AIC: Akaike information criterion; BIC: Bayesian information criterion.

Appendix 2 Comparison of studies

Study	Our Study (Taiwan)	Su et al. (USA)	Chiang et al. (Hong Kong)	Wen et al. (China & USA)
Perspective	NHI perspective	Payer Perspective	Payer Perspective	Payer Perspective
Time horizon	20 years	Not report	5 years	10 years
Discount rate	3%	3%	3%	3%
Incremental cost (NTD/USD)	NT$1,867,151	$89,807	$79,074	$77,139 (China) $89,056 (USA)
Incremental QALYs	0.53	0.53	0.439	0.53
ICER (NTD/USD per QALY)	NT$3,523,768	$169,223	$179,729	$145,546 (China) $168,030 (USA)
WTP threshold (NTD/USD)	NT$2,788,290	$150,000	$100,000 $150,000	$28,527 (China) $150,000 (USA)

ICER, incremental cost-effectiveness ratio; NHI, National Health Insurance; QALYs, quality-adjusted life years; WTP, willingness to pay.

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