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Cost-effectiveness of benmelstobart and anlotinib plus chemotherapy as first-line therapy for extensive-stage small cell lung cancer in China

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The results of the ETER701 trial showed that benmelstobart and anlotinib plus chemotherapy have potential advantages in the treatment of extensive small cell lung cancer (ES-SCLC). However, it must be noted that the high cost cannot be ignored. This study was designed to assess the cost-effectiveness of benmelstobart (B) and anlotinib (A) plus etoposide and carboplatin (EC) as first-line treatment options for patients with ES-SCLC in China. From the perspective of Chinese healthcare system, a three-state partitioned survival model was employed. The cycle length was set at three weeks, and the time horizon of the study was set as lifetime horizon. Total costs, life years (LYs), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) as primary outputs of the model. Among them, the cost, and utility values were respectively derived from the YAOZHI database, and published literature on the subject. At the same time, in order to assess the impact of parameter uncertainty on the model outputs, scenario and sensitivity analyses were carried out. The results showed that compared with the EC group, the ICER for the B + A + EC group was $141,623.44/QALY, and the ICER for the A + EC group was $45,353.46/QALY, which were both higher than the willingness-to-pay (WTP) threshold ($38,024.68/QALY). Sensitivity analysis verified the robustness of the model. Scenario analysis showed that charitable donations and cut-price could raise the likelihood of being cost-effective for benmelstobart and anlotinib. B + A + EC and A + EC are considered unlikely to be cost-effective strategies for first-line treatment of ES-SCLC in China. However, reducing the costs of benmelstobart and anlotinib may enhance the cost-effectiveness of these treatment regimens.

Keywords Cost-effectiveness, Benmelstobart, Anlotinib, Extensive-stage small cell lung cancer, Partitioned survival model, First-line

Lung cancer is one of the main causes of death globally in recent years due to its high incidence and fatality. Each year, there are 1.8 million fatalities that may be attributable to lung cancer, and there are 2.2 million new instances of the condition that are diagnosed[1]. Small-cell lung cancer (SCLC), which represents about 10–15% of all cases of lung cancer, was characterized by an exceedingly unfavorable prognosis. The survival rate for SCLC was less than 7% over a period of five years[2]. It is important to note that most patients with SCLC were diagnosed with an extensive stage at the time of diagnosis[3–5]. The chemotherapy regimen consisting of etoposide and platinum chemotherapy is now the standard treatment for extensive small cell lung cancer (ES-SCLC), which serves as the cornerstone of first-line therapeutic treatments[1,6].

Nevertheless, the survival percentage for patients with ES-SCLC treated with standard chemotherapy was just 2% after five years, and the patients' survival only lasted 8 to 10 months[7–9]. For the first time, the IMpower133 trial from 2018 showed that patients with ES-SCLC might have a much higher chance of survival when using PD-L1 inhibitors in conjunction with chemotherapy, with a median overall survival (OS) of more than a year[10]. Although immunotherapy combined with chemotherapy has brought a historic breakthrough for SCLC, various

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studies (including IMpower133, CASPIAN, CAPSTONE-1, and ASTRO-005) have shown that the median OS can only improve for about 2 to 4 months[11–14], which still cannot meet the urgent need of patients to improve survival. Therefore, it is urgent to explore a more effective treatment method in order to effectively extend patients' lives and enhance their quality of life[15].

Benmelstobart is a highly stable and high-affinity humanized IgG1 subtype PD-L1 inhibitor[16]. Taking into consideration the outcomes of the ETER701 clinical study, benmelstobart was granted approval for use as the first-line therapy for SCLC in May of 2024 [17]. The ETER701 trial results have shown that the new four-drug combination model of adding multi-target anti-angiogenesis drugs on the basis of immunocombined chemotherapy provides a better choice for the first-line treatment of ES-SCLC. The results showed a significant extension of the median OS of patients treated with the four-drug combination group of B + A + EC relative to EC alone (19.32 months vs. 11.89 months), with similar improvements in median progression-free survival (PFS, 6.93 months vs. 4.21 months); In addition, the median OS of patients receiving the three-drug combination of anlotinib plus etoposide and carboplatin had improved (13.27 months vs. 11.89 months), and PFS was significantly prolonged (5.62 months vs. 4.21 months).

Although the survival benefits of benmelstobart and anlotinib in ES-SCLC patients are encouraging, their high costs cannot be ignored, and their economics are not clear. Therefore, this study conducted to evaluate the cost-effectiveness of benmelstobart and anlotinib as a first-line treatment for ES-SCLC patients was evaluated from the perspective of the Chinese health care system. Our main objective is to provide a reference basis for treatment decisions for ES-SCLC patients. At the same time, by exploring the affordable benmelstobart price for untreated ES-SCLC patients in China, we can provide a reference for national medical insurance decision-making.

Results

Base-case results

The base-case results were shown in Table 1. Compared to the EC group, the B + A + EC group had higher gains in life expectancy and quality of life, with an increase of 0.78 LYs (2.07 vs. 1.29 LYs) and 0.44 QALYs (1.03 vs. 0.59 QALYs), but an increase in total costs of $61,923.05 ($71,722.19 vs. $9,799.14). Meanwhile, the A + EC group had an increase in health outputs and costs of 0.17 LYs (1.46 vs. 1.29 LYs), 0.15 QALYs (0.74 vs. 0.59 QALYs), and $6,516.81 ($16,315.95 vs. $9,799.14), respectively, compared to the EC group. Compared with the EC group, the ICER for the A + EC group was $45,353.46/QALY, and the ICER for the B + A + EC group was $141,623.44/QALY, which were both higher than the WTP threshold ($38,024.68/QALY) in this analysis.

Sensitivity analysis results

Based on the results of the OWSA (Fig. 1), it can be seen that the cost of benmelstobart, the utility values of PFS, the discount rate, and the utility values of PD are the factors that have the greatest impact on the cost-effectiveness results in B + A + EC compared with EC. The utility values of PFS and the cost of anlotinib have the greatest effects on the ICER in A + EC compared with EC. In addition, the model was moderately impacted by the proportion of subsequent BSC.

The scatterplots were shown in Fig. 2. After 5,000 simulations, all ICERs for B + A + EC compared with EC were above the WTP threshold, which suggests that B + A + EC is not economical. However, it can be seen that there is an 10.32% probability that the ICERs in A + EC compared with EC will fall below the WTP threshold. The results of the CEAC (Fig. 3) indicate that B + A + EC corresponds to a 50% economic probability when the WTP

Strategy	Total cost ($)	LYs	QALYs	ICER ($/QALY)
Base-case analysis				
EC	9,799.14	1.29	0.59	-
A + EC	16,315.95	1.46	0.74	45,353.46
B + A + EC	71,722.19	2.07	1.03	141,623.44
Scenario analysis 1				
EC	9,799.14	1.29	0.59	-
A + EC	14,996.60	1.46	0.74	36,171.45
B + A + EC	36,469.21	2.07	1.03	60,996.78
Scenario analysis 2				
EC	9,799.14	1.29	0.59	-
A + EC	14,996.60	1.46	0.74	36,171.45
B + A + EC (B*0.3611)	26,423.62	2.07	1.03	38,021.64
B + A + EC (B*0.15)	23,104.44	2.07	1.03	30,430.38
Scenario analysis 3				
EC	25,211.00	1.29	0.59	-
A + EC	26,810.06	1.46	0.74	11,128.57
B + A + EC	80,428.80	2.07	1.03	126,287.95

Table 1. The results in the base-case and scenario analyses. LYs, life years; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; B, benmelstobart; A, anlotinib; EC, etoposide and carboplatin.

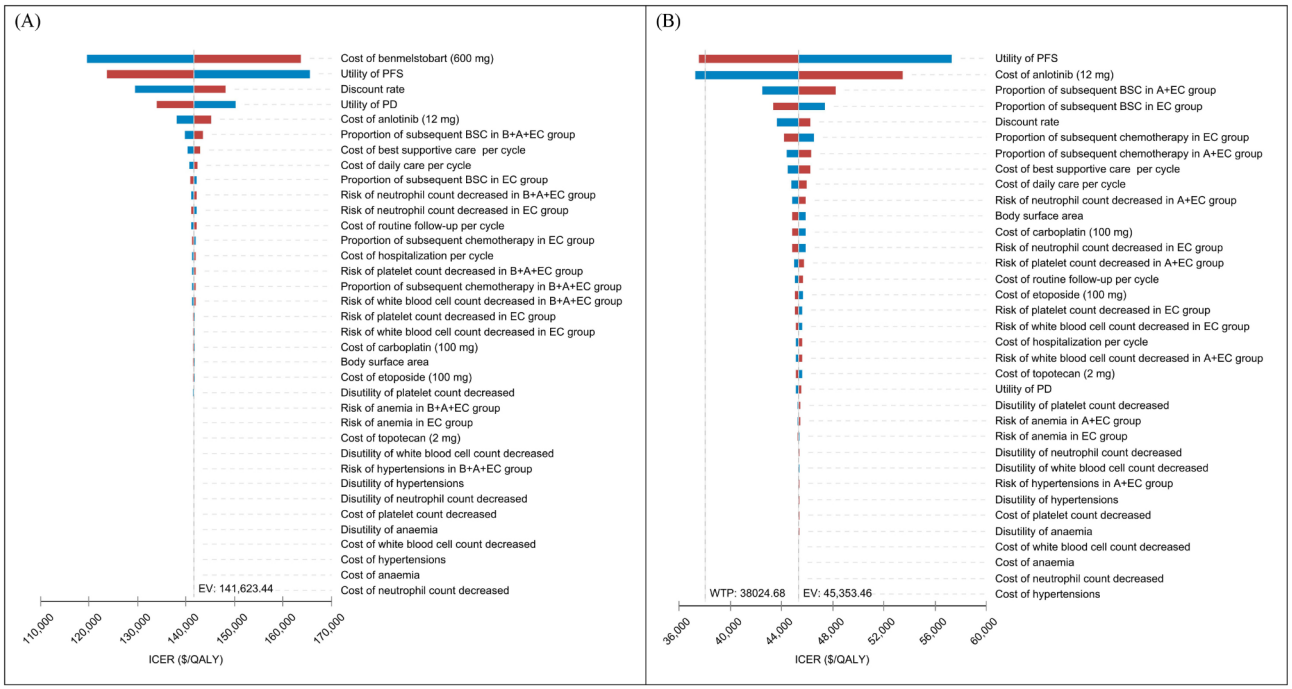

Fig. 1. Tornado diagram of one-way sensitivity analyses of (**A**) B + A + EC vs. EC and (**B**) A + EC vs. EC. PFS, progression-free survival; PD, progressive disease; EV, expected value; WTP, willingness-to-pay; B, benmelstobart; A, anlotinib; EC, etoposide and carboplatin; BSC, best supportive care.

threshold is $141,623.44/QALY and a 90% economic probability when the WTP threshold is $165,461.47/QALY. The probability of the A + EC group being cost-effective reaches 90% when the WTP threshold is $55,059.73/QALY.

Scenario analyses results

Scenario analysis 1 When all patients are eligible for benmelstobart and anlotinib charitable donations, the total cost of the B + A + EC group ($36,469.21) was $26,670.07 higher than that of the EC group ($9,799.14). The ICER ($60,996.78/QALY) of B + A + EC group in this scenario was still higher than the WTP threshold ($38,024.68/QALY). But the ICER ($36,171.45/QALY) in A + EC compared with EC was below the WTP threshold, with the probability of the A + EC group being cost-effective was 65.24% in this scenario (Supplementary Fig. 3).

Scenario analysis 2 The results of the scenario analysis indicated that when the price of benmelstobart is reduced by 63.89% and patients meet charitable assistance for anlotinib, it would render the regimen of B + A + EC potentially cost-effective (Supplementary Fig. 4). And when the price of benmelstobart is reduced by 85%, the probability of the B + A + EC group being cost-effective reaches 97.66% (Supplementary Fig. 4).

Scenario analysis 3 The results of the scenario analysis showed that changing the rate and type of follow-up treatment had a greater impact on outcomes. In Scenario 3, the total cost of the B + A + EC group ($80,428.80) was $55,217.80 higher than that of the EC group ($25,211.00), and its ICER ($126,287.95/QALY) remained significantly higher than the WTP threshold ($38,024.68/QALY). However, compared to EC, the ICER result for the A + EC group ($11,128.57/QALY) showed a reversal, falling well below the WTP threshold. Under this scenario, the probability of the A + EC group being cost-effective reached 98.56% (Supplementary Fig. 5).

Discussion

As another revolution after immunotherapy, the new treatment mode of adding anti-angiogenic drugs on the basis of immunotherapy combined with chemotherapy has brought new hope to ES-SCLC. The results of the ETER701 trial indicated that B + A + EC was efficacious in the first-line treatment of small cell lung cancer and achieved the best OS benefit in the current ES-SCLC first-line immunotherapy studies. Our study assessed the cost-effectiveness of B + A + EC as well as A + EC for the first-line treatment of ES-SCLC using a PSM based on the results of the ETER701 trial.

The results of the base-case analysis indicated that ICER in the B + A + EC group was significantly higher than the WTP threshold set in this study ($38,024.68/QALY) compared with the EC group, indicating that B + A + EC as a first-line treatment for ES-SCLC is unlikely to be cost-effective when compared with EC in China. The OWSA showed that the price of benmelstobart was the most influential factor in the model, but even so, changes in its price within the set range did not change the results of the economic analysis. Against the backdrop of encouraging drug innovation, the initial launch price of an innovative drug at the beginning of its market launch is generally higher due to the high investment in the R&D phase. benmelstobart was first approved for marketing in China on May 9, 2024, and is currently not in the health insurance catalog. Therefore, in this

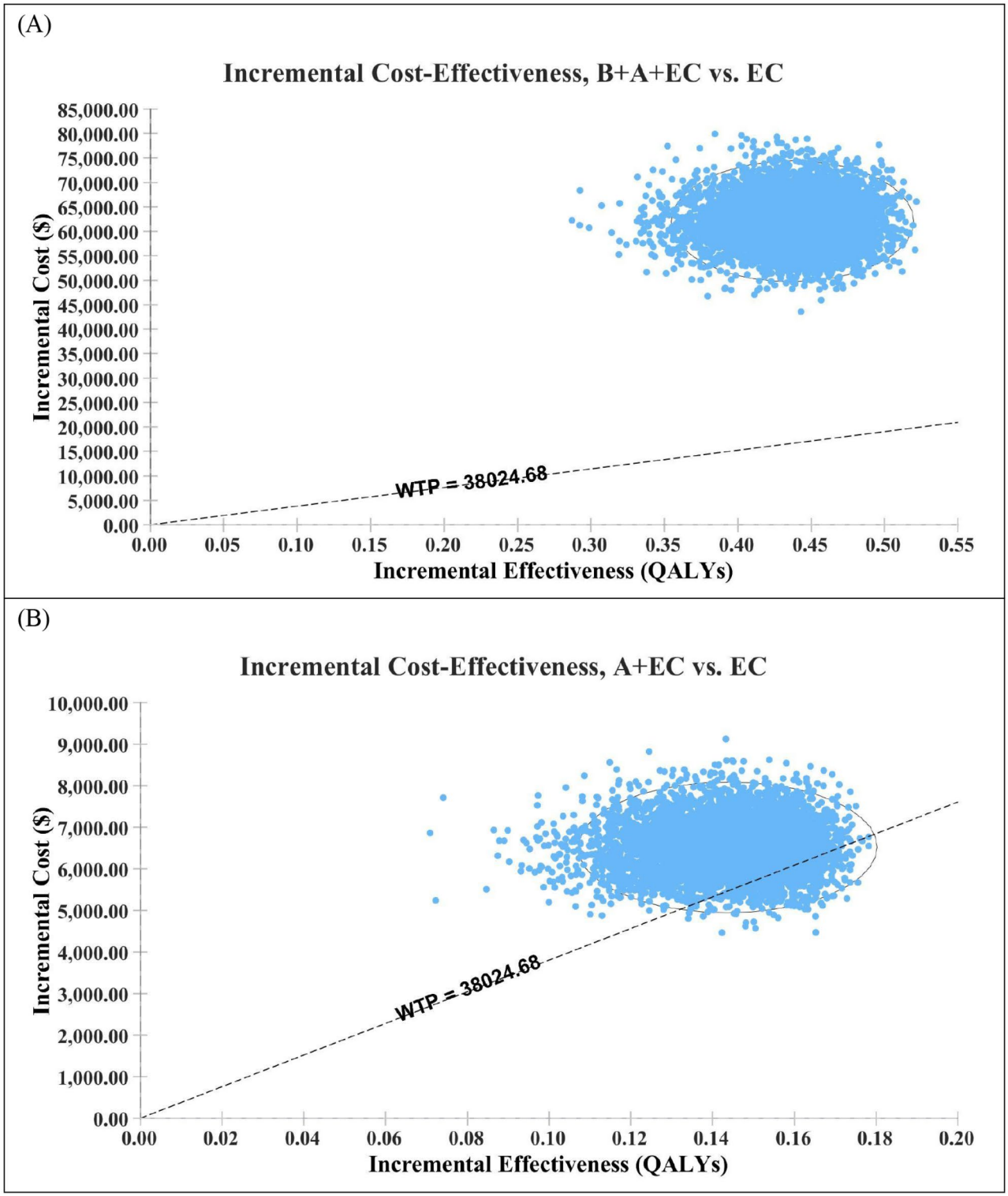

Fig. 2. Scatterplots of the ICER for (**A**) B + A + EC vs. EC and (**B**) A + EC vs. EC. QALYs, quality-adjusted life years; WTP, willingness-to-pay; EC, etoposide and carboplatin.

high pricing scenario, it is difficult for B + A + EC to have a cost-effectiveness advantage over less expensive EC programs. These results were consistent with most cost-effectiveness analyses of immune checkpoint inhibitors (ICIs) combined with chemotherapy, suggesting that it is difficult for newly marketed innovative drugs to be economically viable in cancer treatment[1,3,7,18]. Moreover, the OWSA results indicated that utility values for PFS and PD significantly influenced model outcomes, suggesting that improved patient utility levels could enhance the cost-effectiveness of B + A + EC as a first-line treatment for advanced ES-SCLC. This may be because the

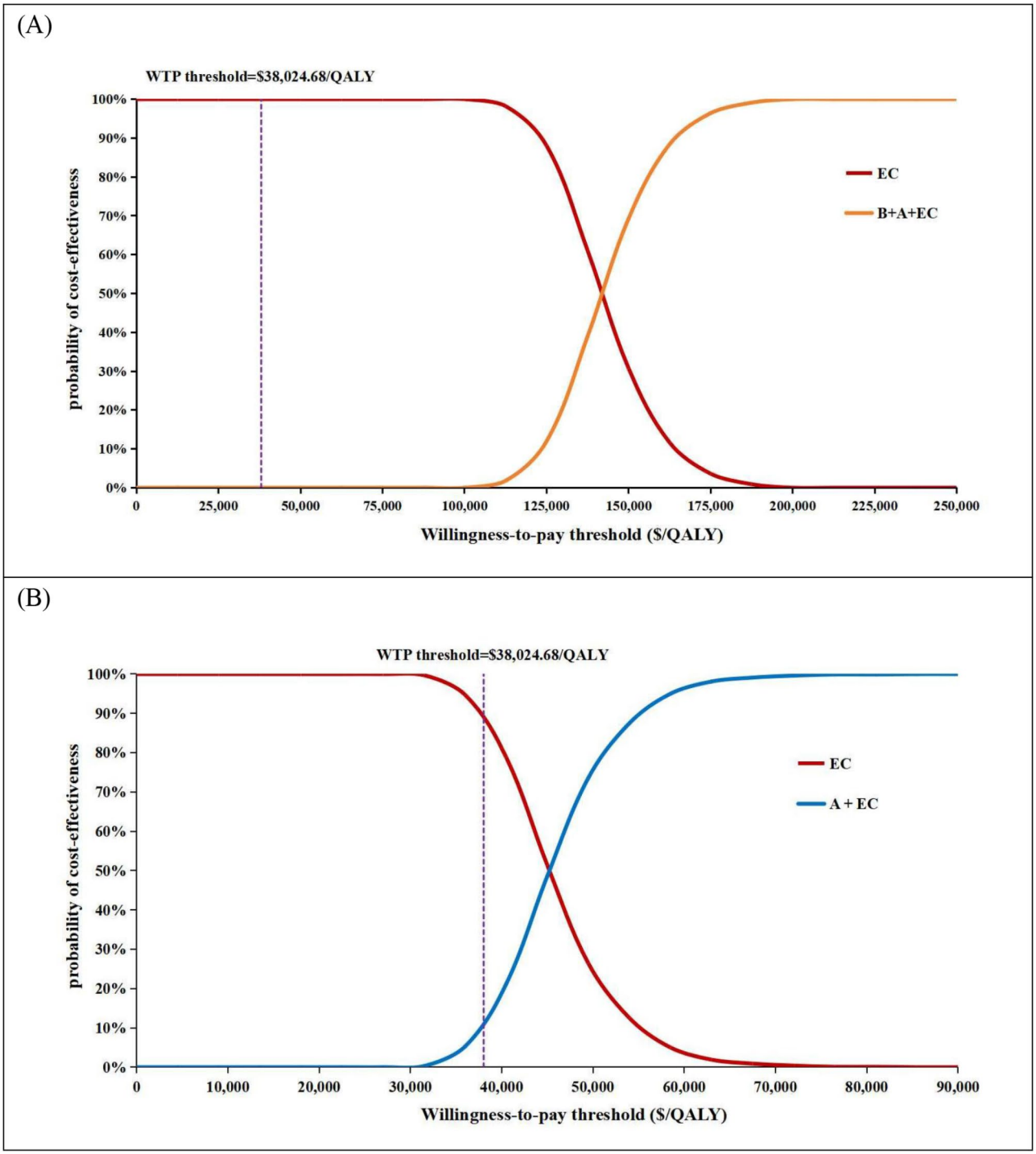

Fig. 3. The cost-effectiveness acceptability curves for (**A**) B + A + EC vs. EC and (**B**) A + EC vs. EC. QALY, quality-adjusted life year; WTP, willingness-to-pay; B, benmelstobart; A, anlotinib; EC, etoposide and carboplatin.

B + A + EC group in first-line treatment of advanced SCLC provides patients with significant benefits in OS and PFS compared to the EC group.

The ICER for the A + EC group was $45,353.46 /QALY compared to the EC group, which was also higher than the WTP threshold in this study ($38,024.68 /QALY). This result was inconsistent with previous studies based on anlotinib in third-line cancer patients[19,20]. There are two possible explanations for this inconsistency: (1) In the ALTER 0303 [21] and ALTER1202 [22] studies, anlotinib was compared with placebo in third-line and above treatment, while in the ETER701 study, chemotherapy regimen was used as the control group, so anlotinib was more effective than placebo. (2) Compared with the survival benefit of anlotinib in third-line and above

treatment (mOS, 9.6 months or 7.3 months), anlotinib + EC in first-line treatment can significantly improve the OS of cancer patients (13.27 months). The total cost of treatment associated with it also increases significantly.

According to the OWSA results, both the costs of benmelstobart and anlotinib have significant influences on the analysis results of this model. Therefore, this study also analyzed the economics under the assumption that all patients met benmelstobart and anlotinib charitable gift conditions. The results showed that ICER ($36,171.45/QALY) in the A + EC group was lower than the WTP threshold compared to EC. Even in the case of donation, ICER ($60,996.78/QALY) in the B + A + EC group was still higher than the WTP threshold ($38,024.68/QALY) and still did not have an economic advantage compared with EC. As far as we know, China's independently developed PD-1 inhibitors, such as camrelizumab and sintilimab, were initially priced at $2,861.48/200 mg and $1,132.74/100 mg, respectively. However, after health insurance negotiations, the prices were reduced to $423.15/200 mg and $156.08/100 mg, respectively, a reduction of more than 85%. Therefore, this study further analyzed the economic benefits of B + A + EC in the first-line treatment of patients with ES-SCLC by assuming a reduction in the price of benmelstobart. The results of scenario analysis 2 indicate that the B + A + EC may be cost-effective when the price of benmelstobart is reduced by 63.89%. When the price of benmelstobart is reduced by 85%, the probability of cost-effectiveness of group B + A + EC reaches 97.66%. It is reasonable to expect that with future economic growth and policy advancements, the cost-effectiveness of B + A + EC could improve significantly.

We believe that the reason why B + A + EC and A + EC do not have a cost-effective advantage in this study is related to lower WTP value in addition to the higher price of the drugs themselves. The WTP value used in this study ($38,024.68/QALY) is 3 times the per capita GDP commonly used in China, while the ICER value of anti-tumor drugs such as benmelstobart is about twice that of other drugs due to high development costs and other factors. In some developed countries, such as the United States, when evaluating the economic benefits of drugs, the WTP value of anti-tumor drugs ($100,000 ~ $150,000 /QALY) is on average higher than that of other drugs ($50,000 /QALY)[1,23]. If the WTP value of China's anti-tumor drugs adopts a higher threshold compared with other drugs, the economy of the B + A + EC group in this study will be significantly improved.

To simplify the model, this study referred to the CSCO guidelines and NCCN guidelines, and assumed in the base analysis that the treatment regimen after disease progression was topotecan only, without considering individual differences. However, additional subsequent treatment options have been published in the ETER701 trial. This study also performed a scenario analysis by varying the proportions and types of subsequent treatments. In scenario analysis 3, the B + A + EC group showed significant differences in subsequent treatment regimen selection compared with the EC group: the proportion of immunotherapy was 13.01% vs. 21.46% (B + A + EC group vs. EC group), respectively, while the proportion of targeted therapy amounted to 15.04% vs. 29.55%. Notably, the A + EC group also showed a decreasing trend in the selection of subsequent immunotherapy (16.73% vs. 21.46%) and targeted therapy (21.22% vs. 29.55%). In contrast, the cost of receiving immunotherapy and targeted therapy was higher according to the current standard of care. It suggests that the dynamics of subsequent treatment regimens in cost-effectiveness analysis models are a key sensitivity factor affecting the results of economic assessments, as these parameters can significantly affect the total cost of disease progression. Therefore, with the accumulation of data on real-world treatment patterns, the future should aim to further validate the cost-effectiveness of combination chemotherapy with benmelstobart and anlotinib as a first-line treatment for ES-SCLC when more publicly available data on subsequent treatments become available to improve the cost-effectiveness assessment system.

The study has the following limitations: First, the long-term survival data were extrapolated from short-term K-M curves, so our reliance on survival modeling to simulate data outside of the trial follow-up period may introduce an inherent bias compared to actual long-term survival data. Second, only serious adverse events with an incidence greater than 5% were considered, although sensitivity analysis showed that adverse event related parameters (including incidence and administrative costs) had little impact on the results. Third, due to the lack of international study data on utility values for SCLC, this study used utility values for NSCLC as an alternative. Therefore, a higher ICER may be caused by the higher malignancy and lower actual utility of SCLC, compared with NSCLC. In addition, the SCLC utility value should be further studied in the future to improve the accuracy and reliability of the model. Fourth, referring to published papers, we simplified the model by assuming patients' body weight of 65 kg, body surface area of 1.72 m^2, and creatinine clearance of 70 ml/min. OWSA showed that these parameters had less impact on the model results, indicating that the model remained robust and reliable under these assumptions. Last, this study used published economic literature to identify some important cost variables, rather than real-world health care data. However, the OWSA showed that the model results were not sensitive to other costs except anlotinib costs.

Methods

This study complied with the updated reporting criteria of the Consolidated Health Economic Evaluation Reporting Standards as shown in Supplementary Tables 1 [24].

Model overview

The population included in this study were patients with pathologically proven ES-SCLC who had not previously received systemic therapy for the disease, which were in alignment with the patients recruited in the ETER701 [17] trial. Eligible patients in ETER701 trial with ES-SCLC were randomized (1:1:1) to receive B (benmelstobart, 1200 mg, day 1) + A (anlotinib, 12 mg, days 1–14) + E (etoposide, 100 mg/m^2, days 1–3) + C (carboplatin, area under the concentration-time curve (AUC) = 5 mg/mL/minute, day 1) or placebo + A + EC or placebo + EC for four 21-day cycles, then received B + A, placebo + A, or placebo maintenance therapy until progress or toxicity tolerance. According to the ETER701 trial, it was assumed that 42.7%, 58.4%, and 71.3% of patients in B + A + EC, A + EC, and EC groups would receive second-line chemotherapy after progression, respectively. The remaining

patients in each group were assumed to receive best supportive care (BSC). According to the recommendation of the Chinese Society of Clinical Oncology Guidelines (CSCO) (2024), topotecan (1.25 mg/m^2, day 1–5) was selected as the second-line chemotherapy in this study[25](Supplementary Table 4).

This study used TreeAge software (TreeAge Pro 2020, https://www.treeage.com) to construct a three-state partitioned survival model (PSM) that included progression-free survival (PFS), progressive disease (PD), and death[26](Supplementary Fig. 1). The cycle length was set at three weeks, according to the treatment regimen of ETER701 trial, and the time horizon of the study was set as lifetime horizon. It was assumed that all patients entered the model in a state of PFS. The proportion of patients in each health state was obtained according to the OS curve and PFS curve in ETER701 trial, respectively. Costs and health outcomes were discounted at 5% [27], and the willingness-to-pay (WTP) threshold was set as three times gross domestic product (GDP) per capita in 2023 ($38,024.68/quality-adjusted life-year (QALY))[28,29], as recommended by the "China Guidelines for Pharmacoeconomic Evaluations (2020)".

Clinical data inputs

At first, the GetData Graph Digitizer software (version 2.24) was used to extract the data of the OS and PFS Kaplan-Meier (KM) survival curves from the ETER701 trial. Then, using R software (version 4.2.3), the individual patient data (IPD) were reconstructed according to the Guyot method[30]. Further, the survival curves were fitted separately using the generalized gamma, weibull, gompertz, exponential, log-logistic, gamma and log-normal distributions. Finally, the best-fitting distribution was considered to extrapolate the survival curves based on the Akaike information criterion (AIC), Bayesian information criterion (BIC), and visual inspection[31]. Supplementary Table 2 displayed the goodness-of-fit results, whereas Supplementary Table 3 summarized the shape parameters (γ) and scale parameters (λ) of the optimal distributions. The fitting extrapolated long-term survival curves were presented in Supplementary Fig. 2.

Cost inputs

This study was conducted from the perspective of the Chinese healthcare system. Therefore, only the costs directly related to medical care—such as those associated with medication, routine follow-up, adverse events (AEs) management, best supportive care, hospitalization and daily care—were taken into account in this study. Of these, the unit prices for benmelstobart, anlotinib, carboplatin, etoposide and topotecan were derived from the average prices in the YAOZHI database (https://data.yaozh.com/)[32]. In order to calculate the cost per cycle of the drug, we assumed that all the patients in this study had a body surface area of 1.72 m^2, a body weight of 65 kg and a creatinine clearance of 70 ml/min[33,34]. Only the costs of serious (grade ≥ 3) and ≥ 5% incidence of AEs were considered in this study[4,35]. In the ETER701 trial, only the overall incidence rate of adverse reactions has been reported. The model was unable to accurately simulate the time of occurrence of adverse reactions and the costs incurred. Consequently, the costs of AEs in this model were considered by multiplying the single-treatment costs by the incidence of AEs and assumed to be incurred only during the first cycle. Other costs were obtained from the published literature[4,25,36]. Each cost was converted to US dollars, using the exchange rate of $1 = 7.05 CNY (2023). The related data were shown in Table 2.

Utility inputs

As health utility evaluations were not assessed in ETER701 trial and there are no studies on SCLC utility values, utility values from published studies on non-small cell lung cancer (NSCLC) were used in this study. Therefore, in this model, the health utility values for PFS and PD states were 0.804 and 0.321, respectively[5], while the disutility values for main AEs were obtained from the published literature in this study[5,37]. All of the parameters were also shown in Table 2.

Sensitivity analyses

One-way sensitivity analysis (OWSA) was performed by setting the range of variation of various parameters in the model and presenting the results in the form of tornado diagrams. According to the "China Guidelines for Pharmacoeconomic Evaluations (2020)", the discount rate varied from 0 to 8% [22]. We assumed that the upper and lower limits of the other parameters are 80% ~ 120% of the baseline value[38,39]. In addition, based on the parameter ranges and distributional forms, 5,000 Monte Carlo simulations were carried out to investigate the impact on model uncertainty when multiple parameters were changed simultaneously. We assumed that the cost parameters obeyed a gamma distribution, whereas parameters such as health utility values and adverse event rates obeyed a beta distribution. Then the results of probabilistic sensitivity analysis (PSA) were shown as scatterplots and cost-effectiveness acceptability curves (CEACs).

Scenario analysis

This study also analyzed the following two hypothetical scenarios:

Scenario analysis 1 Benmelstobart is sold at a higher price and is not yet covered by China's healthcare security. However, to alleviate the financial burden on patients, a charitable grant program on benmelstobart has now been launched. The drug donation scheme of benmelstobart is "2 + 2, 2 + 12", meaning that patients who purchase 2 cycles of benmelstobart can receive 2 cycles of drug assistance. Patients can then receive 12 assistance cycles after buying another two cycles, and subsequent cyclic applications according to this scheme. Anlotinib is currently not reimbursed through healthcare security for the first-line treatment of small-cell lung cancer, but assistance is also currently available to patients through a charitable gift program. Patients can receive 8 cycles of drug assistance if they purchase 10 cycles of benmelstobart, and they can receive 13 cycles of aid after purchasing an additional 5 cycles according to the "10 + 8, 5 + 13" drug donation plan for anlotinib. It is assumed

Parameters	Baseline value	Range		Distribution	Reference
		Minimum	Maximum		
Cost inputs (US $)					
Benmelstobart per 600 mg	1741.84	1393.48	2090.21	Gamma	Local Charge
Anlotinib per12mg	40.21	32.17	48.26	Gamma	Local Charge
Carboplatin per 100 mg	23.13	18.51	27.76	Gamma	Local Charge
Etoposide per 100 mg	13.63	10.90	16.35	Gamma	Local Charge
Topotecan per 2 mg	14.56	11.64	17.47	Gamma	Local Charge
Best supportive care per cycle	328.45	262.76	394.14	Gamma	(4)
Routine follow-up cost per cycle	157.25	125.80	188.70	Gamma	(19)
Hospitalization per cycle	58.78	47.02	70.53	Gamma	(19)
Daily care per cycle	134.93	107.94	161.92	Gamma	(30)
Cost of SAEs per unit					
Neutrophil count decreased	86.16	68.93	103.39	Gamma	(3)
Platelet count decreased	1078.44	862.76	1294.13	Gamma	(3)
White blood cell count decreased	476.81	381.45	572.17	Gamma	(3)
Anaemia	519.99	415.99	623.98	Gamma	(3)
Hypertensions	16.22	12.98	19.47	Gamma	(29)
Risk for SAEs in B + A + EC group					
Neutrophil count decreased	0.695	0.556	0.834	Beta	(17)
Platelet count decreased	0.496	0.397	0.595	Beta	(17)
White blood cell count decreased	0.382	0.306	0.458	Beta	(17)
Anaemia	0.240	0.192	0.288	Beta	(17)
Hypertensions	0.155	0.124	0.186	Beta	(17)
Risk for SAEs in A + EC group					
Neutrophil count decreased	0.730	0.584	0.876	Beta	(17)
Platelet count decreased	0.537	0.430	0.644	Beta	(17)
White blood cell count decreased	0.307	0.246	0.368	Beta	(17)
Anaemia	0.266	0.213	0.319	Beta	(17)
Hypertensions	0.119	0.095	0.143	Beta	(17)
Risk for SAEs in EC group					
Neutrophil count decreased	0.687	0.550	0.824	Beta	(17)
Platelet count decreased	0.358	0.286	0.430	Beta	(17)
White blood cell count decreased	0.346	0.277	0.415	Beta	(17)
Anaemia	0.236	0.189	0.283	Beta	(17)
Utility inputs					
Utility of PFS	0.804	0.643	0.965	Beta	(5)
Utility of PD	0.321	0.257	0.385	Beta	(5)
SAEs disutility					
Neutrophil count decreased	0.200	0.160	0.240	Beta	(5,31)
Platelet count decreased	0.190	0.152	0.228	Beta	(5,31)
White blood cell count decreased	0.200	0.160	0.240	Beta	(5,31)
Anaemia	0.073	0.058	0.088	Beta	(5,31)
Hypertensions	0.042	0.034	0.050	Beta	(31)
Others					
Discount rate	0.05	0.00	0.08	Fixed	(21,23)
Body surface area (m^2)	1.72	1.38	2.06	Gamma	(27,28)
Body weight (kg)	65	52	78	Normal	(27,28)
Creatinine clearance rate (ml/min/1.72m^2)	70	-	-	Uniform	(27,28)
Area under the curve (mg/mL/min)	5	-	-	Uniform	(27)

Table 2. Key model inputs. PFS, progression-free survival; OS, overall survival; PD, progressive disease; SAEs, serious adverse events; B, benmelstobart; A, anlotinib; EC, etoposide and carboplatin.

that all patients in this scenario will be able to apply for assistance through the charitable grant program for benmelstobart and anlotinib.

Scenario analysis 2 We performed a scenario analysis on the price of benmelstobart to determine the price reduction required for the B + A + EC regimen to become cost-effective. In addition, a growing number of immune

checkpoint inhibitors (ICIs) have been admitted to China's health insurance through National Reimbursement Drug list (NRDL) negotiation, with a price cut of up to 85% [40]. Thus, we assessed the likelihood that B + A + EC would be cost-effective by assuming an 85% reduction in the price of benmelstobart. And it is assumed that in this scenario, all patients would be qualified for charitable assistance for anlotinib at the same time.

Scenario analysis 3 Considering the uncertainty of subsequent treatment and the possibility that patients may also choose other drugs in addition to Topotecan, such as immunotherapy and targeted therapy, this study performed a scenario analysis by varying the proportions and types of subsequent treatment. However, as the ETER701 trial only provided treatment categories without specifying particular drugs and there was treatment crossover[17]. Therefore, this study selected treatments according to the guidelines of the CSCO and the National Comprehensive Cancer Network (NCCN) and made the following assumptions: topotecan as a chemotherapy, anlotinib as a targeted therapy, and pembrolizumab as an immunotherapy. Due to the wide variation in individualization of traditional chinese medicine (TCM), and the fact that no studies on second-line TCM for ES-SCLC have been searched. Moreover, in the ETER701 trial, the proportion of patients who received TCM as second-line treatment was relatively small. We did not consider TCM as a subsequent treatment in this study. Patients not receiving further systemic therapy in the ETER701 trial are assumed to receive best supportive care. The maximum use of immunotherapy (pembrolizumab) is 24 months according to clinical guidelines, and patients will receive best supportive care if immunotherapy is continued beyond 24 months. Costs of relevant subsequent treatment drugs were obtained from the YAOZHI database (https://data.yaozh.com/), and costs of radiotherapy were taken from the average of the three commonly used radiotherapies in the reference[41] (Supplementary Table 5).

Ethics statement

All the data included in this analysis were derived from published literature and public data. No patient-identifiable data were applied or used. Therefore, institutional review board approval was not required.

Conclusion

In summary, the combinations of B + A + EC and A + EC as the first-line treatment option for ES-SCLC were not cost-effective strategies from the perspective of the Chinese healthcare system. In order to make these options more cost-effective, one possible approach would be to lower the prices of benmelstobart and anlotinib.

Data availability

No datasets were generated or analysed during the current study.

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Author contributions

C.Y.Y., Z.X.L., Q.Z. and S.Q.L. were responsible for study design and statistical analysis. C.Y.Y. and J.Y.L. prepared the manuscript. R.G.D., Z.X.L., and W.X.C. searched literatures and collected data, C.Y.Y. and S.Q.L. worked on the survival analysis of reconstructed patient-level data. All authors critically reviewed the methods of analysis, verified results and revised the manuscript. All authors contributed to the article and approved the submitted version.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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