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Cost-effectiveness of acalabrutinib monotherapy or with obinutuzumab versus chemoimmunotherapy for untreated chronic lymphocytic leukemia in China

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Abstract

Background: Acalabrutinib is a highly selective, latest generation Bruton's tyrosine kinase inhibitors for the treatment of chronic lymphocytic leukemia (CLL). The ELEVATE-TN trial (NCT02475681) found significant benefits achieved by the acalabrutinib regimen compared to the chemoimmunotherapy regimen chlorambucil plus obinutuzumab in treatment-naïve CLL. The objective of this study was to explore the cost-effectiveness of acalabrutinib in the first-line treatment of CLL in the light of Chinese healthcare system.

Methods: We constructed a 4-week partitioned survival model and a 20-year lifetime horizon to estimate the cost and utility associated with CLL treatment. The survival data, direct medical costs, and utilities came from the ELEVATE-TN trial, YAOZHI database, and published literatures. The outputs of the model including total costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) were calculated. One-way, probabilistic sensitivity, and scenario analyses were conducted to assess the robustness of the model.

Results: Over a 20-year lifetime horizon, treatment with acalabrutinib + obinutuzumab provided an additional 2.51 QALYs versus treatment with chlorambucil and obinutuzumab, while incurring incremental costs of $940,543 and an ICER of $374,449/QALY. Acalabrutinib had an incremental cost of $683,640 and provided an additional 2.24 QALYs, resulted an ICER of $305,562/QALY. One-way sensitivity analyses suggested that the model was most sensitive to utility of progression-free survival, progression disease, and the cost of acalabrutinib. Probabilistic sensitivity analyses showed that at the willingness-to-pay (WTP) threshold, the probabilities of the acalabrutinib regimens were at an absolute disadvantage. The scenario analyses showed altering the lifetime horizon or price of acalabrutinib did not reverse results of our model.

Conclusion: Acalabrutinib with or without obinutuzumab might not be a cost-effective option in recent China, when compared with chemoimmunotherapy for first-line patients with CLL at the commonly WTP threshold. It is therefore necessary to reduce the price of acalabrutinib.

Plain language summary

Cost-effectiveness of acalabrutinib monotherapy or with obinutuzumab versus chemo-immunotherapy for untreated chronic lymphocytic leukaemia in China

Background: Acalabrutinib is a highly selective, latest generation Bruton's tyrosine kinase inhibitors (BTKis) for the treatment of chronic lymphocytic leukemia (CLL). The objective of this study was to explored the costeffectiveness of acalabrutinib in the first-line treatment of CLL in the light of Chinese healthcare system. Methods: We constructed a 4 weeks partitioned survival model and a 20-year lifetime horizon to estimate the cost and utility associated with CLL treatment. The survival data, direct medical costs and utilities came

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Keywords: acalabrutinib, BTKis, chronic lymphocytic leukemia, cost-effectiveness, partitioned survival model

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Introduction

Chronic lymphocytic leukemia (CLL) is a B-cell malignancy that is generally considered incurable,[1] which characterized by a progressive accumulation of leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues.[2] CLL remains the most prevalent adult leukemia in Western countries, with a significantly higher incidence than in Asian.[3] It has been reported that in 2022 about 20,160 people in the United States will be diagnosed with CLL and 4410 will die from the disease.[4] In addition to regional influences, age also affects morbidity, as the incidence of CLL is expected to increase as the population ages.[5] In China, the median age at onset of CLL was between 58 and 62 years old earlier than the United States, where the median age ranged from 67 to 72.[6]

Bruton's tyrosine kinase inhibitors (BTKis) a novel agents, have become the standard treatment of CLL.[7] Compared with chemoimmunotherapy, BTKis have its unique benefits, such as easy to use and low toxicity. Acalabrutinib is a second-generation BTKis, an oral therapy approved by the US Food and Drug Administration (FDA) for mantle cell lymphoma on October 31, 2017. ELEVATE-TN was a global, phase III, multicenter, open-label study in patients with treatment-naïve CLL done at 142 academic and community hospitals in 18 countries at an initial median follow-up of 28.3 months.[8] The ELEVATE-TN trial demonstrated that acalabrutinib significantly improved progression-free survival (PFS) and overall survival (OS). Based on these results, FDA approved acalabrutinib for adults with CLL or small lymphocytic lymphoma on November 21, 2019. In China, the first approval of acalabrutinib until March 21, 2023, which means that acalabrutinib could be expensive and place a huge burden on patients. With the poor accessibility of acalabrutinib, the guideline of Chinese Society of Clinical Oncology for the diagnosis and treatment of hematological malignancies has recommended acalabrutinib as a first-line treatment option for CLL as level III recommendation,[9] whereas the National Comprehensive Cancer Network recommended acalabrutinib with or without obinutuzumab was a preferred regimens in the first-line treatment.[7]

Despite the favorable clinical efficacy of acalabrutinib in the treatment of CLL, to our knowledge,

its cost-effectiveness has not been evaluated in China. The healthcare resources of China are more scarce than those of developed countries, thus economic evaluation is important to help clinicians and policymakers optimize resource allocation.

The objective of our study is to estimate the cost-effectiveness of acalabrutinib regimens versus chlorambucil with obinutuzumab as first-line treatment of CLL patients on the basis of the ELEVATE-TN trial under Chinese healthcare system.

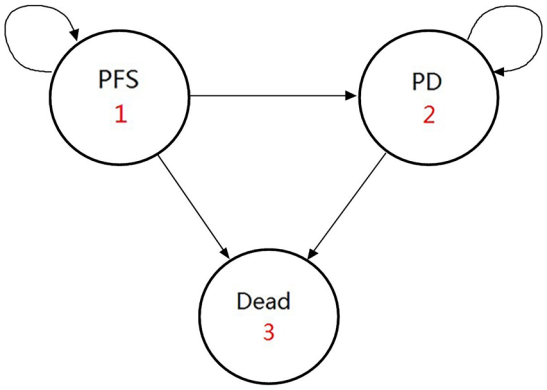

Figure 1. The partitioned survival model consisting of three health states.
PD, progression disease; PFS, progression-free survival.

Methods

Patients and treatment

This study is in compliance with the updated Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) guidelines (Supplemental Table 1). The patient model for CLL with presumed treatment-naïve CLL was consistent with the patients studied in the ELEVATE-TN trial with an overall population median age of 70 years, 39% were female, 63% had an unmutated immunoglobulin heavy chain variable (IGHV) gene, 11% had an mutated TP53, and 9% had a 17p deletion. The demographic and disease characteristics of baseline were similar between groups, such as genetic-molecular prognostic factors. Total patients of 69% had a CLL international prognostic index score of high risk, and 12% had a score of very high risk. A total of 535 patients were randomly assigned to three treatment regimens, of which 179 patients were treated with acalabrutinib–obinutuzumab (AO), 179 patients with acalabrutinib, and 177 patients with obinutuzumab–chlorambucil (OC).

As for the intervention, oral acalabrutinib was administered (100 mg) twice a day up to disease progression or unacceptable toxicity. Obinutuzumab and chlorambucil were administered for six fixed cycles. In the AO group, intravenous obinutuzumab was given on days 1 (100 mg), 2 (900 mg), 8 (1000 mg), and 15 (1000 mg) of cycle 2 and on day 1 (1000 mg) of cycles 3–7. In the OC group, intravenous obinutuzumab was given on days 1 (100 mg), 2 (900 mg), 8 (1000 mg), and 15 (1000 mg) of cycle 1 and on day 1 (1000 mg) of cycles 2–6. Oral chlorambucil was given (0.5 mg/kg) on days 1 and 15 of 1–6 cycle. The clinical trial made no mention of post-progression therapy; therefore, we assumed these patients would receive the treatment recommended by the Chinese guidelines.

Model construction

The study developed a partitioned survival model in TreeAge Pro (TreeAge Software, Inc. 2022R1.2) to compare the cost-effectiveness of AO or acalabrutinib versus OC for CLL under China healthcare system and consists of different health states: PFS, progression disease (PD), and death (Figure 1). The proportion of patients alive was estimated by the area under the OS curve, and the proportion alive on PFS was estimated by the area under the PFS curve. With regard to the PD state, we calculated its proportion from the difference between the PFS and OS curves. Adverse effects (AEs) were also included, we only considered the cost and disutility of grade 3 and higher AEs with a ⩾5% incidence in the trial. IPDfromKM was used to extract the OS and PFS data from Kaplan–Meier curves.[10] R software (4.3.0) was used to additional statistical analyses to identify the best-fitting parameter distributions of survival curve from Weibull, Exponential, Gamma, Log-logistic, and Lognormal distributions, based on the Akaike and Bayesian information criteria as well as visual inspection (Supplemental Figure 1 and Table 2).

The results of the model were used to calculate an incremental cost-effectiveness ratio (ICER) for each strategy, which reflects the cost for each additional quality-adjusted life-year (QALY)

gained due to treatment, in 2022 US dollars (1$ = 6.73 CNY).[11] In this model, a lifetime horizon of 20 years was assumed basing on the age of onset of the disease in the population and life expectancy in China, as well as other literatures in CLL populations.[12,13] The cycle length was 4 weeks (28 days), which is consistent with the administration cycles of ELEVATE-TN. Referring to the China Guidelines for Pharmacoeconomic Evaluations (2020), the willingness-to-pay (WTP) threshold was three times China's per capita GDP, and both costs and utilities discounted at a rate of 5% annually.[14]

Cost inputs

This analysis was conducted from the perspective of the Chinese healthcare system. The cost mainly included drug acquisition, drug administration (only IV drugs), laboratory tests, radiographic examinations, AEs, subsequent treatment, and terminal care (Table 1).

The price of drugs were came from the YAOZHI database, which had the most up-to-date prices available around the country.[15] Our prices were accessed on July 2, 2023. The body surface areas of Chinese patients was about 1.72 m^2 and weighed 65 kg for the dosage of treatment.[16]

In each group, the frequency of laboratory work, computed tomography, or magnetic resonance imaging examination was referred to the ELEVATE-TN trial and Chinese guidelines of hematological malignancies. AEs were assumed to occur in the first cycle and were calculated as a weighted average of the number of adverse reactions reported in clinical trial, including anemia, diarrhea, infusion-related reaction, neutropenia, pneumonia, and thrombocytopenia. All of these costs were retrieved from previously published literatures and local hospital.[17–20] Once the patient has progressed, subsequent treatment would be based on guidelines, with payment rates based on the Diagnosis-Related Groups (DRG) payment standard of China.[21]

Utility inputs

The utility values for PFS and PD and the disutility values for AEs were derived from the published literatures,[22,23] regardless of treatment arm because these were the same utilities for the target population (Table 1). The utility value of PFS and PD were 0.748. and 0.600, respectively. For the death status, the utility value is 0.

Sensitivity analyses

We performed sensitivity analyses to evaluate uncertainty in our model. A one-way sensitivity analyses was conducted by varying key model parameters to determine the impact on the ICER. Typically, parameters used to restrict the range by 95% CI. When 95% CI were unavailable, the variation was made using ±20% of the reference value. The discount rate in one-way analyses ranged from 0% to 8%. One-way sensitivity analyses were presented by a tornado diagram to show the impact of the different parameters variation on the ICER.

Probabilistic sensitivity analyses (PSA) were performed 10,000 Monte Carlo simulations, each time randomly sampling from the prespecified distributions. Costs were assigned with Gamma distributions, and probabilities and utilities were assigned with beta distributions. The PSA was presented by an ICER scatter plot and a cost-effectiveness acceptability curve (CEAC) designed to describe the possibility of preference of strategies.

To assess the sensitivity to long-term survival outcomes of our model, we also performed several scenario analyses using different time horizons (10, 30 years), decreased price by 60% of acalabrutinib and real-world AE management costs.

Results

Base-case analyses

In comparison with OC, AO associated with an incremental cost of $940,543, incremental QALYs gained of 2.51, with a resulting ICER of $374,449/QALY. Compared with OC, acalabrutinib associated with an incremental cost of $683,640, incremental QALYs gained of 2.24, with a resulting ICER of $305,562/QALY (Table 2). According to the base-case analysis, both the ICERs of AO and acalabrutinib were much higher than the specified WTP threshold ($38,201).

One-way sensitivity analyses

The one-way sensitivity analyses for AO versus OC showed that the parameters with the largest

Table 1. Key model inputs.

Parameter	Base case	Range		Distribution	Source
		Minimum	Maximum		
Clinical input					
Survival model for acalabrutinib–obinutuzumab					
Exponential model for PFS	Rate = 0.003,039,91			Fixed	/
Exponential model for OS	Rate = 0.001,767,41			Fixed	/
Survival model for acalabrutinib monotherapy					
Exponential model for PFS	Rate = 0.006,193,95			Fixed	/
Exponential model for OS	Rate = 0.002,348,52			Fixed	/
Survival model for obinutuzumab–chlorambucil					
Weibull model for PFS	Shape = 1.797,311,97 Scale = 0.002,269,72			Fixed	/
Exponential model for OS	Rate = 0.003,704,57			Fixed	/
Costs input ($)					
Acalabrutinib (100 mg)	94.46	75.57	113.35	Gamma	15
Obinutuzumab (1000 mg)	1392.12	1113.70	1670.55	Gamma	15
Chlorambucil (2 mg)	0.93	0.74	1.11	Gamma	15
Cost of laboratory tests per cycle	32.095,096,58	25.676,077,27	38.514,115,9	Gamma	Local hospital
Cost of CT scan	177.265,973,3	141.812,778,6	212.719,168	Gamma	Local hospital
Cost of administration	3.57	2.856	4.284	Gamma	Local hospital
Cost of anemia	2150.12	1720.096	2580.144	Gamma	17
Cost of diarrhea	155	124	186	Gamma	18
Cost of infusion-related reaction	754.82	603.856	905.784	Gamma	19
Cost of neutropenia	1094.28	875.424	1313.136	Gamma	17
Cost of pneumonia	1229.23	983.384	1475.076	Gamma	17
Cost of thrombocytopenia	1415.63	1132.504	1698.756	Gamma	17
Cost of progression	19,613.670,13	15,690.936,1	23,536.4041,6	Gamma	21
Cost of terminal care	1460.3	1168.24	1752.36	Gamma	20
Utility value					
Utility in PD	0.6	0.48	0.72	Beta	22
Utility in PFS	0.748	0.5984	0.8976	Beta	22

(Continued)

Table 1. (Continued)

Parameter	Base case	Range		Distribution	Source
		Minimum	Maximum		
Disutility of anemia	−0.09	−0.072	−0.108	Beta	22
Disutility of diarrhea	−0.2	−0.16	−0.24	Beta	22
Disutility of infusion-related reaction	−0.032,48	−0.025,984	−0.038,976	Beta	22
Disutility of neutropenia	−0.16	−0.128	−0.192	Beta	22
Disutility of pneumonia	−0.2	−0.16	−0.24	Beta	23
Disutility of thrombocytopenia	−0.11	−0.088	−0.132	Beta	22
Others					
Body surface area (m^2)	1.72	1.376	2.064	Gamma	16
Discount rate (%)	5%	0%	8%	Fixed	14

OS, overall survival; PD, progression disease; PFS, progression-free survival.

Table 2. The cost and outcome results of the cost-effectiveness analysis.

Group	*C* ($)	Incr *C*	*E* (QALY)	Incr *E*	ICER ($/QALY)
Chlorambucil + Obinutuzumab	34,614.49		7.7906936		
Acalabrutinib + Obinutuzumab	975,157	940,542.5	10.302497	2.511803	374,449.1
Acalabrutinib monotherapy	718,254.1	683,639.6	10.028016	2.237322	305,561.5

impact on the ICERs were the utility of PFS, PD, and the cost of acalabrutinib, same as the treatment of acalabrutinib versus OC (Figures 2 and 3). All parameters were well above the WTP threshold, indicating that our results were robust.

Probabilistic sensitivity analyses

Results of PSA were presented as an ICER scatter plot and a CEAC (Figures 4–7). According to the scatter plot, compared with OC, all scatter points of AO or acalabrutinib were located in the upper left and above the WTP threshold.

CEAC revealed that compared to OC, at a WTP threshold of approximately $350,000 per QALY, the probability of AO being cost-effective treatment was 50%. At a WTP threshold of approximately $300,00 per QALY, the probability of acalabrutinib being cost-effective treatment was 50%.

Scenario analyses

When the time horizon was 10 or 30 years, AO versus OC resulting in an ICER of $575,585 or $288,549 per QALY. For acalabrutinib versus OC resulting in an ICER of $426,583 or $238,376 per QALY. When the price of acalabrutinib decreased by 60%, compared with OC, AO, and acalabrutinib separately resulted in the ICERs of $149,563 and $119,496 per QALY. Combined with real-world AE management costs, AO and acalabrutinib resulted in the ICERs of $374,492 and $305,660 per QALY, respectively, compared to OC. In scenario analyses, the ICERs for AO

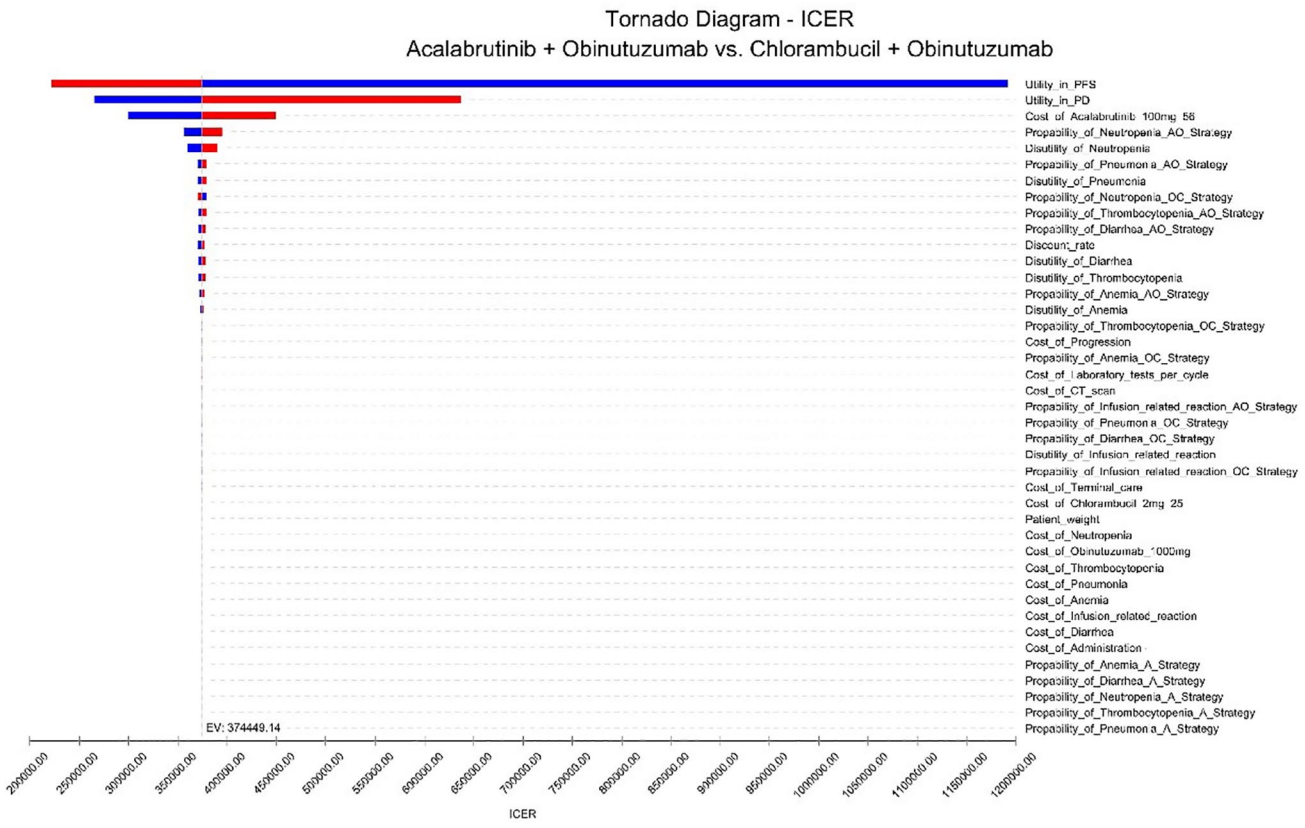

Figure 2. Tornado diagrams of one-way sensitivity analyses of AO versus OC.
AO, acalabrutinib–obinutuzumab; CT, computed tomography; ICER, incremental cost-effectiveness ratios; OC, obinutuzumab–chlorambucil; PD, progressive disease; PFS, progression-free survival.

and acalabrutinib were gradually decreased, but always above the WTP threshold, for both time horizon lengthened and lower prices of acalabrutinib. In scenario where real-world data was used, the ICERs did not differ from our initial result.

Discussion

To our knowledge, this is the first cost-effectiveness study comparing acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for previously untreated CLL in China. In this study, we aimed to evaluate the cost-effectiveness of acalabrutinib for CLL. Our analysis found that AO and acalabrutinib resulted in ICERs of $374,449/QALY and $305,562/QALY, respectively, compared to OC, which are well above the WTP threshold. From the perspectives of health services in China, the results of our study show that no matter AO or acalabrutinib were not cost-effective in Chinese patients.

The results of one-way sensitivity analyses and PSA validated our results were generally robust. The ICERs were sensitive to utility values for PFS, PD health states, and the cost of acalabrutinib. The PSA demonstrated that at a WTP threshold of $38,201, the probability of cost-effectiveness for AO, and acalabrutinib were at an absolute disadvantage. These results suggested that acalabrutinib was not an economical option in the current Chinese healthcare system. From the CEAC, we can infer that at a WTP threshold of $1,000,000 per QALY, the probability of AO being cost-effective treatment was 80%, acalabrutinib being cost-effective treatment was 86%.

Furthermore, we assumed that acalabrutinib will drop in price. Ibrutinib was the first BTKis to hit the market and is currently priced at 31% of its initial launch price.[24] Obinutuzumab is a glyco-engineered type II anti-CD20 monoclonal antibody that has lower complement-dependent

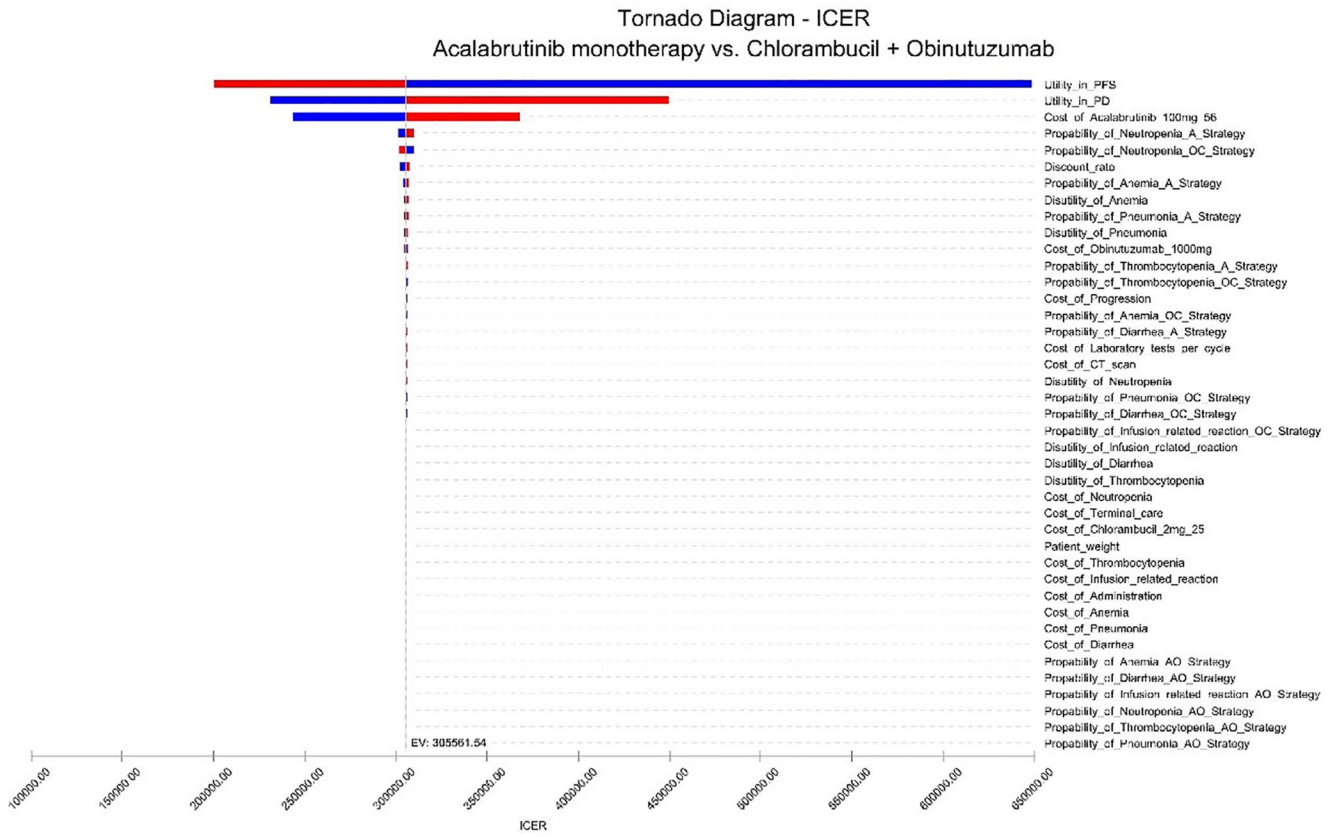

Figure 3. Tornado diagrams of one-way sensitivity analyses of acalabrutinib monotherapy versus obinutuzumab–chlorambucil.
A, acalabrutinib monotherapy; CT, computed tomography; ICER, incremental cost-effectiveness ratio; OC, obinutuzumab–chlorambucil; PD, progressive disease; PFS, progression-free survival.

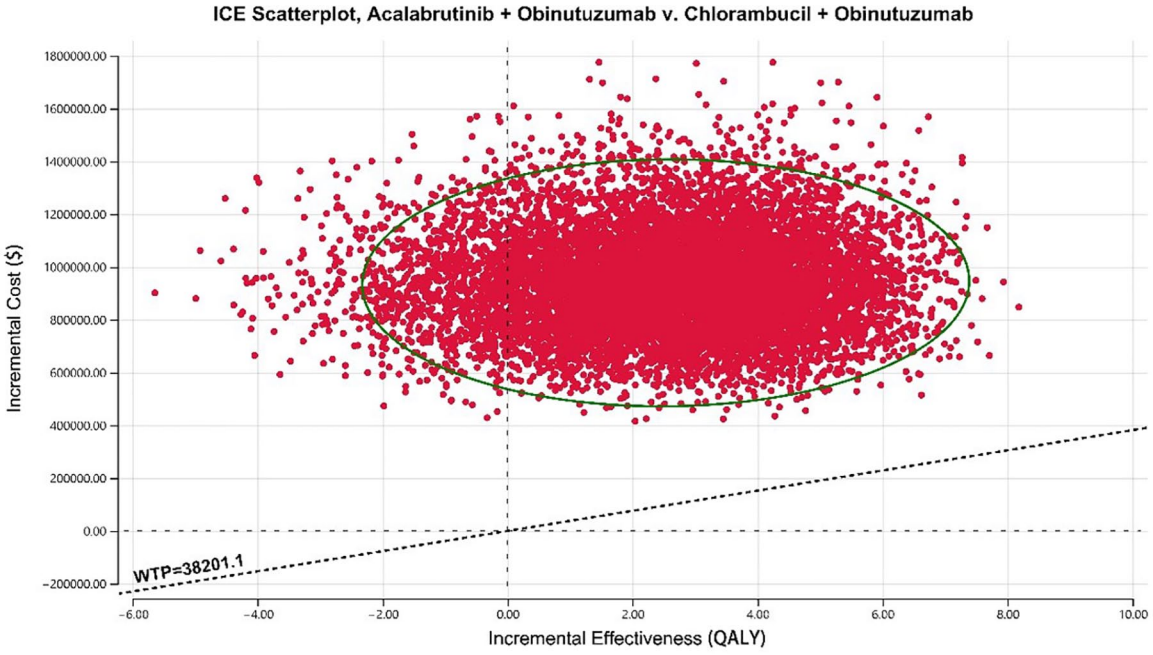

Figure 4. A probabilistic scatter plot of the ICER between acalabrutinib–obinutuzumab and obinutuzumab–chlorambucil.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WTP, willingness-to-pay.

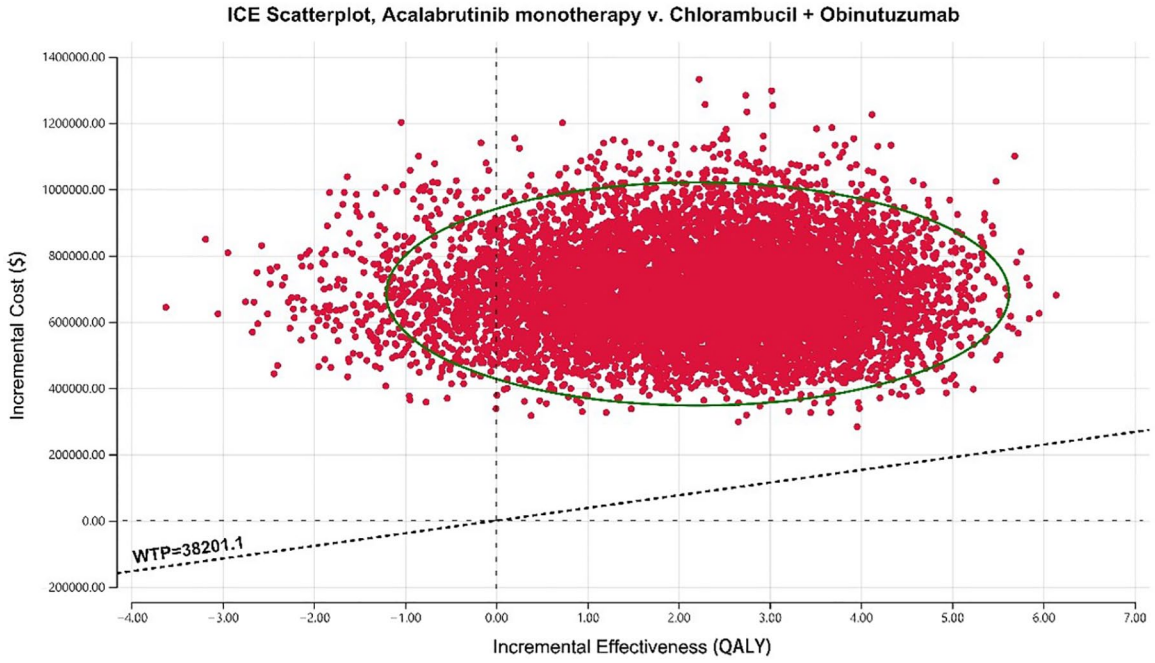

Figure 5. A probabilistic scatter plot of the ICER between acalabrutinib monotherapy and obinutuzumab–chlorambucil.
ICER, incremental cost-effectiveness ratio; WTP, willingness-to-pay; QALY, quality-adjusted life-year.

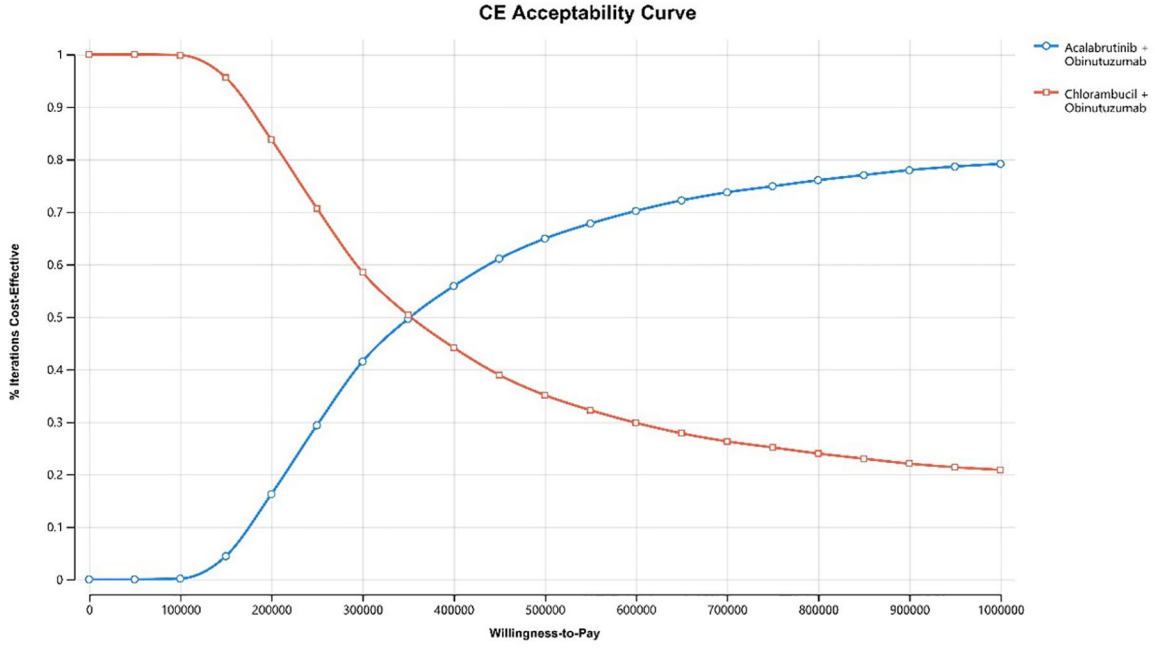

Figure 6. Cost-effectiveness acceptability curve for acalabrutinib–obinutuzumab versus obinutuzumab–chlorambucil.

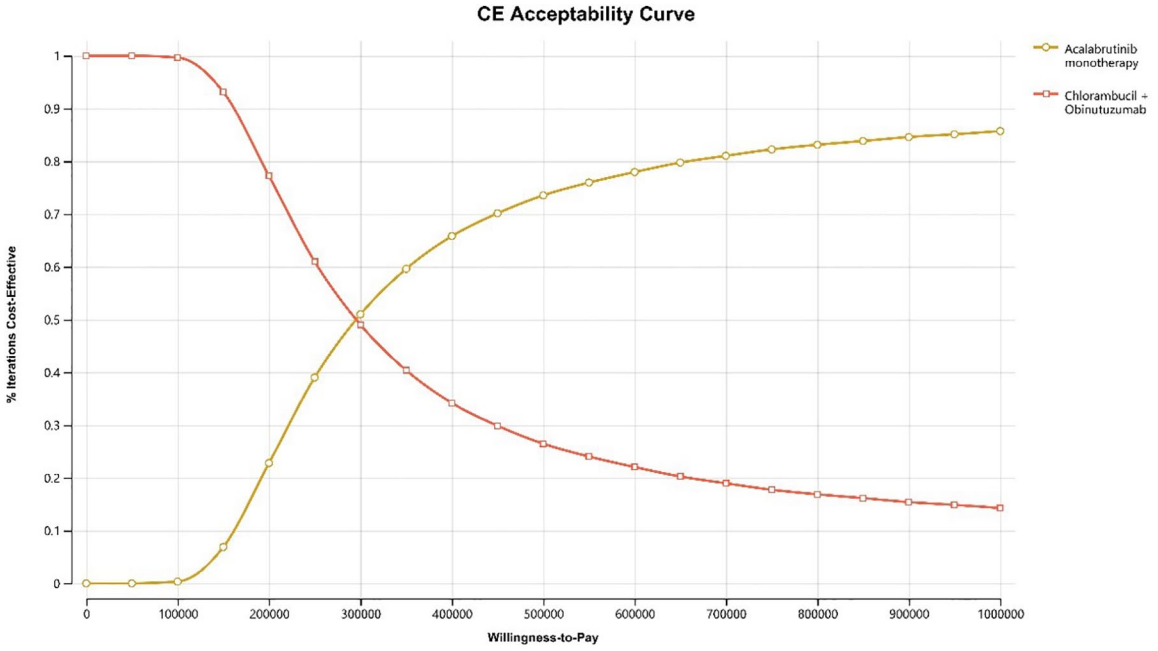

Figure 7. Cost-effectiveness acceptability curve for acalabrutinib monotherapy versus obinutuzumab–chlorambucil.

cytotoxicity but strong antibody-dependent cellular cytotoxicity.[25] Glycosylation modification of obinutuzumab at the Fc segment enhances its affinity for immune effector cells, thereby enhancing antibody-dependent cell-mediated cytotoxicity and phagocytosis,[26] which antitumor activity has been observed in patients with CLL,[27] and cut price by more than 60% in less than a year since first marketed in China. Taking into account the decrease in drug prices, we assumed that acalabrutinib would drop in price by 60% in a short period of time, then we found in scenario analyses our model affirmed stable. To demonstrate the reliability of our study, we also used real-world AE management costs and found that our conclusions were still robust.

The huge amount of money spent on research before a new drug is released on the market causes new drugs to be far more expensive than those that already exist.[28] Malignancy drugs are the area where most research advances are being made, and new drugs are commonly used in oncology patients, but expensive prices significantly reduce the accessibility of these drug. Therefore, it is important to weigh the pros and cons as high prices can place a heavy financial burden on patients. Since 2017, China has implemented combined medication price negotiation and mandatory reimbursement policies for targeted anticancer medications,[29] these measures may further reduce the national drug price which is known as national drug price negotiation (NDPN). NDPN has improved access and affordability of expensive targeted anticancer drugs by reducing the cost per unit of drug and increasing utilization, benefiting many patients.

A similar model was developed under a US Medicare,[22] the results from that study found treatment with acalabrutinib at $81,960/QALY is cost-effective compared with OC, whereas the cost-effectiveness of treatment for AO was $152,153/QALY, which is slightly above the WTP threshold ranging from $100,000/QALY to $150,000/QALY. Another economic study under UK perspective indicated acalabrutinib was marginally cost-effective when compared with OC, resulting in an ICER of £30,701 per QALY.[30] Both studies were broadly similar to our findings, and even in developing countries, acalabrutinib did not have a complete absolute advantage. Hence, authors suggests lowering price or offering a complimentary drug program to improve the probability of the economics of acalabrutinib.

A major strength of our analysis is that we used efficacy and safety modeling data from a direct comparison in the ELEVATE-TN trial, which was a head-to-head comparison between acalabrutinib regimens and chemoimmunotherapy. Besides, the model is the first cost-effectiveness study about acalabrutinib in China, and considering that there are multiple BTKis for sale today, this article may provide ideas for acalabrutinib to win the Chinese market.

There are several limitations that need to be noted in this study. First, the utility of PFS and PD was retrieved from the literature, which may have led to the deviations of our conclusion. Another limitation is that all patients who enrolled in ELEVATE-TN trial were from outside of China. There may be some individual differences, such as racial differences and age of disease. Additionally, an immaturity of the follow-up data from the trial required extrapolation, which introduces uncertainty about long-term outcomes. In the follow-up analyses of ELEVATE-TN, the median follow-up time for patients receiving long-term therapy was 46.9 months, and long-term outcomes in the model are still immature.[31] Future studies with longer trial follow-up and more mature survival data may help to confirm longer-term cost benefits of acalabrutinib. Fourth, not all adverse reactions were included in the model, and we only considered adverse reactions of grade 3 or higher; therefore, we may have overestimated the advantages and underestimated the costs. Finally limitation is that acalabrutinib and obinutuzumab currently not approved by the National Medicinal Products Administration in China, acalabrutinib and obinutuzumab can off-label use as first-line treatments for CLL. With the Law on Doctors of the People's Republic of China passed on August 20, 2021, off-label use of drugs has been included into the legislation for the first time China passed.

Conclusion

In summary, the results of this cost-effectiveness model indicated that acalabrutinib with or without obinutuzumab were not a cost-effective option in China, when compared with chemoimmunotherapy for first-line patients with CLL at a WTP threshold of $38,201 per QALY.

Declaration

Ethics approval and consent to participate

Ethics approval for this study was not required per the authors' hospital regulations.

Consent for publication

Not applicable.

Author contributions

Mengya Li: Formal analysis; Software; Writing – original draft; Funding acquisition.

Xiaoyan Zhong: Formal analysis; Writing – original draft.

Chengbin Zhang: Data curation; Software.

Hongli Luo: Data curation; Investigation.

Li Luo: Funding acquisition; Supervision.

Yilan Huang: Supervision; Writing – review & editing.

Longyang Jiang: Funding acquisition; Software; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data presented in this study are available on request from the corresponding author.

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Supplemental material

Supplemental material for this article is available online.

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