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Original article

# Ribociclib in hormone-receptor-positive advanced breast cancer: Establishing a value-based cost in China

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ABSTRACT

*Background:* The addition of ribociclib (RIB) to letrozole (LET) significantly increases progression free survival for patients with hormone-receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (ABC). We identified the range of drug costs for which RIB could be considered cost effective from a Chinese perspective.
*Methods:* A discrete event simulation model was developed to model the treatment sequences among patients with ABC. Life years (LYs), quality-adjusted LYs (QALYs) and lifetime costs were estimated. Costs were estimated for Chinese health care systems. Three times the per capita gross domestic product (GDP) of China 2016 ($24,360) and three times the per capita GDP of Beijing city 2016 ($53,384) were used as the willingness-to-pay threshold. Probabilistic sensitivity analyses were performed.
*Results:* In the base case analysis, RIB + LET provided an incremental survival benefit of 0.631 LYs and 0.451 QALYs. When RIB costs less than $721 or $1170 per 4 weeks, there was a nearly 90% likelihood that the incremental cost-effectiveness ratio for RIB + LET would be less than $24,360 per QALY or $53,384 per QALY, respectively.
*Conclusion:* A value-based price for the cost of RIB is $732 or $1170 per 4 weeks for China and Beijing City, respectively. Our study is helpful to inform the multilateral drug price negotiations in China that may be upcoming for RIB.



Breast cancer is the most common cancer and the second leading cause of cancer deaths among women [1]. Up to 80% of breast cancers express the estrogen receptor, progesterone receptor, or both [2]. Endocrine therapies are the standard of care for postmenopausal women with hormone-receptor (HR)-positive advanced breast cancer (ABC) [3]. However, resistance to hormonal blockade develops in the majority of patients, which needs the administration of new approaches. Ribociclib (RIB) is a cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor and has been recommended as preferred regimens for the treatment of postmenopausal women with HR-positive, human epidermal growth factor receptor 2 (HER2)-negative ABC in 2017 based on the results from the MONALEESA-2 trial by The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology [4]. The trial showed improved progression free survival (PFS) for patients with RIB plus letrozole (RIB + LET) versus LET alone (LET) [hazard ratio 0.56; 95% confidence interval 0.43, 0.72], with a median PFS not reached for the RIB + LET arm and 14.7 months for the LET arm [5].

RIB has been approved by the U.S. Food and Drug Administration (FDA) for HR-positive, HER2-negative ABC [6]. RIB has not been marketed in China, however, since the Chinese government reformed the examination and approval system of pharmaceuticals and medical devices in 2015 and 2017, the time to approve the marketing of imported drugs has been greatly shortened and imported drugs will be marketed in China almost simultaneously with other countries (e.g. US). For example, China FDA (CFDA) expanded approved regorafenib (Stivarga) for the treatment of hepatocellular carcinoma in December 2017, only 7 months later than in the US.

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**List of abbreviations**

| | |
|---|---|
| HR | Hormone-receptor |
| ABC | Advanced breast cancer |
| RIB | Ribociclib |
| CDK4/6 | Cyclin-dependent kinases 4 and 6 |
| HER2 | Human epidermal growth factor receptor 2 |
| NCCN | National Comprehensive Cancer Network |
| PFS | Progression free survival |
| FDA | Food and Drug Administration |
| CFDA | China Food and Drug Administration FDA |
| DES | Discrete event simulation |
| AEs | Adverse events |
| LYs | Life-years |
| QALY | Quality-adjusted life-years |
| ICER | Incremental cost-effectiveness ratio |
| FUL | Fulvestrant |
| EVE | Everolimus |
| EXE | Exemestane |
| IPD | Individual patient data |
| OS | Overall survival |
| PSA | Probabilistic sensitivity analyses |
| WTP | Willingness-to-pay |
| QOL | Quality of life |
| PAL | Palbociclib |
| GDP | Gross Domestic Product |

Once the CFDA approves RIB, the treatment costs may substantially increase due to the use of the drug. Therefore, we performed an estimate to identify the range of drug costs from a Chinese perspective within which adding RIB as a first-line treatment for ABC could be considered cost effective.

## 1. Methods

We developed a discrete event simulation (DES) model using TreeAge Pro 2018 software (TreeAge, Williamstown, MA) to model the treatment sequences among postmenopausal women with HR-positive, HER2-negative ABC and establish a value-based cost in China, similar to our previous study [7] (Fig. 1 and Supplementary A). The properties of DES approach include tracking changes in patients' baseline characteristics and treatment history, which make the approach suitable to model cancer treatment sequences [8]. Patients who initially received RIB + LET or LET could end therapy because of disease progression, adverse events (AEs) or death. Upon progression of disease or unacceptable toxicity, patients could receive next-line therapy or no more treatment. The next-line treatment sequence included up to two lines of endocrine therapy and three lines of chemotherapy (Fig. 1 and Supplementary A) according to the NCCN guidelines and a previously published study [4,9].

Both costs and outcomes were discounted by 3% per year. The primary outputs of the models included the total cost, life-years (LYs), quality-adjusted LY (QALY), and incremental cost-effectiveness ratio (ICER). We estimated costs for Chinese health care system perspective. Only direct care costs were considered in the model. All costs in this study are stated in 2015 U.S. dollars and expressed in U.S. dollars with an exchange rate of U.S. \$ 1 = CYN 6.23 (2015).

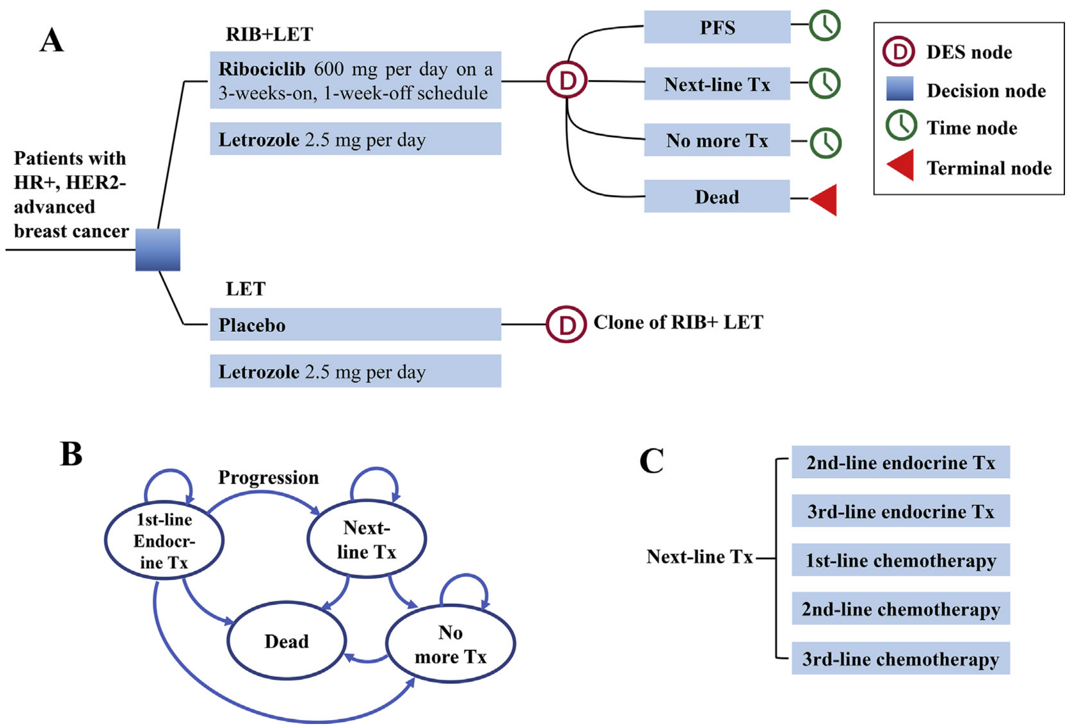


**Fig. 1.** (A) Abbreviated decision tree and discrete event simulation model used to compare two strategies for treating hormone-receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer explored in the MONALEESA-2 trial. (B) Influence diagram shows a network of four health states. (C) Next-line treatment sequence. D, Discrete event simulation model; Tx, Treatment. HR+, Hormone-receptor-positive; HER2-, human epidermal growth factor receptor 2-negative.

### 1.1. Patients and intervention

The assumption on the survival benefit associated with first-line RIB + LET versus LET was based on the results from the MONALEESA-2 trial [5]. Eligible patients had either measurable ABC according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) or at least one predominantly lytic bone lesion and have not received prior systemic therapy for advanced disease. Patients were randomly assigned to receive RIB + LET or LET [5].

After disease progressed, following the approach of Mamiya et al. [9], both groups received next-line treatments as follows: fulvestrant (FUL) as second-line endocrine therapy, everolimus (EVE) plus exemestane (EXE) as third-line endocrine therapy, and three lines of chemotherapy.

### 1.2. Progression risk

The estimates of progression risk for treatment with RIB + LET or LET were based on the results of the MONALEESA-2 trial [5]. First, we used Digitizer software (version 2.3.3; https://www.digitizeit.de/) to extract the PFS probabilities from the PFS curves. Next, pseudo individual patient data (IPD) were generated using the algorithm derived by Hoyle et al., which improves estimates accuracy of mean survival time which are essential for cost-effectiveness analysis [10,11]. A Weibull distribution was fitted to the pseudo IPD data and the shape parameter ($\gamma$) and scale parameter ($\lambda$) were estimated.

We estimated the progression risks for patients receiving next-line endocrine therapies using the same approach with the PFS curves from previous phase 3 clinical trials [2,12]. The progression risks for three lines of chemotherapy were estimated assuming an exponential distribution based on the median PFS reported by an observational study [13]. The rates of any grade 3 or 4 AEs occurring for patients during each line of therapies in the model were based on the reported frequency of AEs in the published clinical trials [2,5,12,14]. The proportion of patients who received next-line therapies following progression of disease during each line of therapies was estimated based on previous observational and randomized trial [13,15].

### 1.3. Mortality estimates

The mortality rate for patients who received no more therapy was based a previous study [9]. The background mortality rate for Chinese women was derived from Chinese life table [16].

### 1.4. Costs and utilities

Direct costs regarding drug, administration, and AEs were considered (Table 1). The drug costs were based on the following

**Table 1**
Model parameters and assumptions.

| Cost | Mean ($) | Distribution | Reference |
|---|---|---|---|
| LET/4 weeks | 560.3 | γ(100, 0.178) | Local charge |
| FUL/injection | 771.0 | γ(100, 0.130) | Local charge |
| EVE/4 weeks | 1661.6 | γ(100, 0.060) | Local charge |
| EXE/4 weeks | 214.8 | γ(100, 0.466) | Local charge |
| FUL administration | 19.8 | γ(100, 5.051) | Local charge |
| Toll for major toxicity/one time cost | 369.2 | γ(100, 0.271) | [18] |
| Chemotherapy/month | 1070.1 | γ(100, 0.093) | [18] |
| Toll for death/one time cost | 6445.7 | γ(100, 0.016) | [17] |

| Variable | RIB + LET | Distribution | Reference | LET | Distribution | Reference |
|---|---|---|---|---|---|---|
| Mean PFS (month) | | Weibull (scale, shape) | | | Weibull (scale, shape) | |
| First-line endocrine therapy | 28.31 | (0.0108,1.2507) | [5] | 18.91 | (0.0191, 1.2717) | [5] |
| Second-line endocrine therapy | 4.86 | (0.07877, 1.5094) | [2] | 4.86 | (0.07877, 1.5094) | [2] |
| Third-line endocrine therapy | 12.82 | (0.0272, 1.3660) | [12] | 12.82 | (0.0272, 1.3660) | [12] |
| Median PFS (month) | | Hazard rate = λ | | | Hazard rate = λ | |
| First-line chemotherapy | 7.1 | λ = β (90, 833) | [13] | 7.1 | λ = β (90, 833) | [13] |
| Second-line chemotherapy | 3.7 | λ = β (81, 352) | [13] | 3.7 | λ = β (81, 352) | [13] |
| Third-line chemotherapy | 3.3 | λ = β (79, 296) | [13] | 3.3 | λ = β (79, 296) | [13] |
| Incidence of any grade 3 or 4 AEs | | | | | | |
| First-line endocrine therapy | 0.812 | β (18, 4) | [5] | 0.327 | β (67, 138) | [5] |
| Second-line endocrine therapy | 0.18 | β (82, 373) | [2] | 0.18 | β (82, 373) | [2] |
| Third-line endocrine therapy | 0.5 | β (50, 50) | [12] | 0.5 | β (50, 50) | [12] |
| Chemotherapy | 0.38 | β (62, 101) | [14] | 0.38 | β (62, 101) | [14] |
| Proportion of discontinuation due to AEs | 0.075 | β (92,1140) | [5] | 0.021 | β (98, 4563) | [5] |
| Proportion of receiving subsequent therapy | | | | | | |
| Second-line endocrine therapy from first-line endocrine therapy | 0.54 | β (45, 39) | [13] | 0.54 | β (45, 39) | [13] |
| Third-line endocrine therapy from second-line endocrine therapy | 0.42 | β (28, 80) | [13] | 0.42 | β (28, 80) | [13] |
| First-line chemotherapy from any endocrine therapy | 0.87 | β (12, 2) | [13] | 0.87 | β (12, 2) | [13] |
| Second -line chemotherapy from any first-line chemotherapy | 0.64 | β (35, 20) | [13] | 0.64 | β (35, 20) | [13] |
| Third -line chemotherapy from any second -line chemotherapy | 0.68 | β (31, 15) | [13] | 0.68 | β (31, 15) | [13] |
| Cancer-specific mortality | 0.5 | β (50, 50) | [9] | 0.5 | β (50, 50) | [9] |
| Background mortality | Chinese life table | – | [16] | Chinese life table | – | [16] |
| Utility | | | | | | |
| Endocrine therapy | 0.7 | β (29, 13) | [9] | 0.7 | β (29, 13) | [9] |
| Chemotherapy | 0.58 | β (41, 30) | [9] | 0.58 | β (41, 30) | [9] |
| AE disutility | −0.28 | β (72, 184) | [9] | −0.28 | β (72, 184) | [9] |
| Terminal disease | 0.23 | β (77, 257) | [9] | 0.23 | β (77, 257) | [9] |

LET = letrozole; FUL= Fulvestrant; EVE = everolimus; EXE = exemestane; PFS= Progression free survival; AE = adverse event.

schedules: RIB (600 mg per day on a 3-weeks-on, 1-week-off schedule), LET (2.5 mg per day), FUL (500 mg every 14 days for the first 3 injections and then every 28 days), EVE (10 mg daily), and EXE (25 mg daily). We included only the costs of management of any grade 3 or 4 AEs in the model.

The costs of drugs and administration were obtained from local hospitals. The cost of chemotherapy for Chinese patients with ABC were adopted from our previously published economic evaluation [17]. The cost of AEs was derived from a published economic evaluation [18]. Drug costs were listed in Table 1.

Previously published mean utilities derived by using visual analog scale and standard gamble were used in the model [9] (Table 1). QALY was calculated by multiplying the utility value by the time spent in a specified health state. The utility decrement associated with AEs was model with a one-time disutility. Constant utilities during endocrine therapy or chemotherapy were assumed regardless of the number of treatment lines.

### 1.5. Model validation

Internal and external model validations were performed. The internal validation showed that the PFS generated by the DES model closely approximated those presented in the clinical trials (Supplementary B). The overall survival (OS) was not reported in the MONALEESA-2 trial, however, the OS curve for the patients receiving LET simulated by our model was compared with those from studies by Finn et al. [19] and Mouridsen et al. [20](Supplementary B). The median survival time of 33.74 months for patients treated with LET simulated by our DES model matched the median OS time of 33.3 months and 34 months reported by Finn et al. [19] and Mouridsen et al. [20], respectively.

### 1.6. Sensitivity analysis

Probabilistic sensitivity analyses (PSA) was performed to assess the robustness of the model and explore uncertainty in estimation of variables. The model was run 1000 times with the parameters simultaneously varied with a specific pattern of distribution. The mean value of each distribution was assumed to be their baseline values and standard error was set at 10% of baseline values. The distributions used in PSA are summarized in Table 1. Curves which represents the probability that the ICER is below the willingness-to-pay (WTP) thresholds for different costs of RIB were presented.

### 1.7. Variations in the cost of RIB

The base case model was run multiple times with different costs of RIB to determine the effect on the ICER, which resulted in ICERs below the WTP threshold were presented.

## 2. Results

### 2.1. Base case results

In the base case analysis, the model projected that the life expectancy of patients receiving RIB + LET was 3.593 LYs, which was 0.631 LYs more than patients receiving LET. Accounting for quality of life (QOL), patients receiving RIB + LET gained 2.293 QALYs; this value was 0.451 QALYs more than for patients receiving LET. When RIB cost $830 and $1320 per 4 weeks, the ICER approximated the WTP threshold of $24,360 per QALY or $53,384 per QALY, respectively (Table 2).

**Table 2**
Incremental difference in base case results at additional modeled ribociclib price points.

| Parameter | Results of base case model analysis, varying only ribociclib cost | |
|---|---|---|
| Willingness-to-pay, $US/QALY | 24,360 | 53,384 |
| Ribociclib cost, $/4 weeks | 830 | 1320 |
| Total cost, $ | 10,881 | 23,935 |
| LYs | 0.631 | 0.631 |
| QALYs | 0.451 | 0.451 |
| ICER, $/LY | 17,224 | 37,932 |
| ICER, $/QALY | 24,126 | 53,071 |

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

### 2.2. Sensitivity analysis

Fig. 2 demonstrates that when RIB cost less than $732 or $1170 per 4 weeks, there was a nearly 90% likelihood that the ICER for RIB + LET would be less than $24,360 per QALY or $53,3834 per QALY, respectively. When the price of RIB was greater than $1776 per 4 weeks, the probability that the ICERs exceeded WTP thresholds in China were 100%.

## 3. Discussion

We performed an evaluation to establish the value-based price for RIB from the Chinese perspective. On the basis of our model, when RIB cost less than $732 or $1170 per 4 weeks in China, there was a nearly 90% likelihood that the ICER for RIB would be less than $24,360 per QALY or $53,384 per QALY, respectively. Previous studies have analyzed the cost-effective of palbociclib (PAL) in ABC which is also a CDK4/6 inhibitor and has been approved by the US FDA for use in women with HR-positive, HER2-negative ABC [9,21]. A US study found that adding PAL to LET for treatment-naive patients cost $768,498/QALY [9], whereas in Canada, it was Canadian $10,999/quality-adjusted life-month [21]. The conclusion of these studies that adding PAL to LET is unlikely to be cost-effective compared with LET agree with that for RIB in our study. In fact, for advanced cancer disease, where patients' survival is limited, not only the CDK4/6 inhibitors, but also many cancer drugs are not cost-effective because of their modest incremental benefits and high incremental costs. Goldstein et al. reported a cost of $571,240 per QALY and $364,083 per QALY for patients treated with first- and

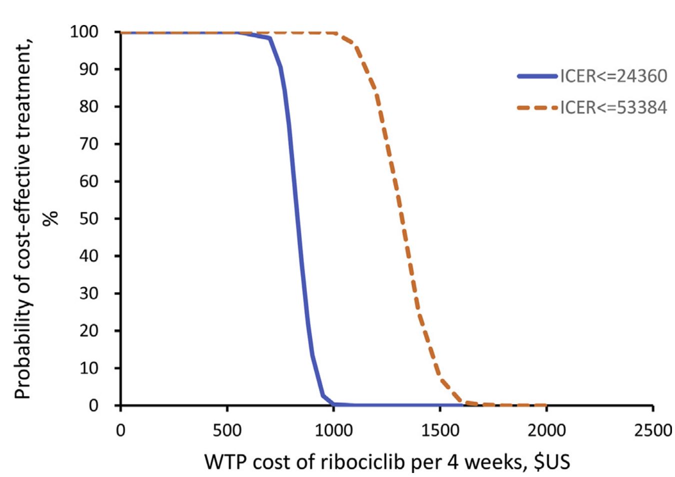


**Fig. 2.** Ribociclib cost-effectiveness curves with different costs for ribociclib. ICER, incremental cost-effectiveness ratio; WTP, willingness-to-pay.

second-line bevacizumab for metastatic colorectal cancer (mCRC), respectively [22]. Another study by Goldstein et al. reported a cost of $900,000 per QALY for patients with regorafenib for mCRC [23]. Durkee et al. reported a cost of $472,668 per QALY for patients with pertuzumab for ABC [24]. These low-value drugs are covered and adopted in the US because Medicare must reimburse any FDA-approved drugs regardless of price, thereby few barriers to coverage and adoption are placed on low-value drugs [25]. As with the US FDA, the CFDA does not consider cost in the evaluation and approval process of new drugs. Many new, innovative cancer drugs are not covered by the National Reimbursement Drug List in China and thereby patients must pay out of pocket. In China, the manufacturers can freely set the patent drug prices, which make the prices too high to afford [7]. Due to the high out-of-pocket costs, patients in China suffer financial toxicity. However, there are signs of progress. Recently, the value-based cancer care and pricing has taken a center stage in academia and cost-effectiveness analysis is considered a standard and well-validated method to examine a care or drug's value. The pricing mechanisms in China have gradually changed to multilateral negotiations since 2015 and economic evaluation is an important content during the multilateral negotiations [7]. Therefore, the results of our study are helpful to inform the multilateral drug price negotiations that may be upcoming for RIB.

We used three times the per capita gross domestic product (GDP) of China 2016 ($24,360) and three times the per capita GDP of Beijing city 2016 ($53,384) as the WTP threshold in China [26], due to the unbalanced development of China's economy, according to the recommendation by World Health Organization. As with any model, there are limitations to our analysis. A specific sequence of treatments following disease progression was assumed in the model, which might be different from that in clinical practice. However, we believe this assumption has little impact on the conclusions of our study because of close approximation of actual PFS and OS. The model was developed based on NCCN guidelines, which may not exactly reflect the clinical practice in China. However, as most oncologists in China make their clinical decisions based on the NCCN guidelines [27], the difference in clinical practice for breast cancer between the US and China has little impact on the conclusions of our study. We considered only grade 3 and 4 events in the model. The inclusion of all AEs in the model would not change the conclusions of the study because the sensitivity analysis revealed that the result is insensitive to changes associated with AEs. The utility values for Chinese patients were derived from published studies, which may not reflect Chinese data. However, we believe that actual variations in QOL have been accounted for in the sensitivity analyses.

The value-based price of RIB established in our study is helpful to inform the multilateral drug price negotiations. The results of our study also contribute to a broader discussion of cost and value in cancer care. As the drug prices dramatically rise, it is particularly important that coverage decisions and pricing should be guided by cost-effectiveness analyses, especially for China where insurance coverage is insufficient and out-of-pocket costs are high. Data from our study and others like it contribute to such discussions.

## Conflicts of interest

XM Wan declares that he has no conflict of interest. YC Zhang declares that he has no conflict of interest. JA Ma declares that he has no conflict of interest. CQ Tan declares that he has no conflict of interest. XH Zeng declares that he has no conflict of interest. LB Peng declares that she has no conflict of interest.

## Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.breast.2018.10.004.

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