# Cost-Effectiveness Analysis of Adding Palbociclib as a Second-Line Endocrine Therapy for HR$^+$/HER2$^-$ Metastatic Breast Cancer From the US and Chinese Perspectives

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## ABSTRACT

**Purpose:** As a second-line endocrine therapy for hormone receptor–positive and human epidermal growth factor receptor 2–negative (HR$^+$/HER2$^-$) metastatic breast cancer, palbociclib has demonstrated significant efficacy in prolonging progression-free survival when added to a regimen containing fulvestrant. The objective of this study was to evaluate the cost-effectiveness of palbociclib from the perspectives of the United States and China.

**Methods:** We developed a Markov model to estimate lifetime costs, overall life-years gained, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs). One-way and probabilistic sensitivity analyses were performed to predict the uncertainty of the model developed. The time horizon was 10 years, and the perspective was that of the payer.

**Findings:** Within a 10-year time horizon, the palbociclib-containing strategy provided an additional 0.568 QALY, with an ICER of 88,854 USD/QALY, in the United States. When palbociclib cost 30%, 20%, and 10% of the current price, the ICERs were 185,526, 42,193, and 98,860 USD/QALY, respectively. In China, the ICER was 182,779 USD/QALY. When palbociclib cost 30%, 20%, and 10% of the current price, the ICERs were 79,558, 64,812, and 50,066 USD/QALY, respectively. In order to meet 50% probability of cost-effectiveness, the estimated price would have to be 32.52 USD/100 mg at a willingness-to-pay threshold of 58,480 USD/QALY (3 × per-capita domestic product of Beijing, China).

**Implications:** Adding palbociclib to a regimen of fulvestrant is unlikely to be cost-effective as a second-line endocrine therapy for HR$^+$/HER2$^-$ metastatic breast cancer (MBC) with at the current price in the United States and China. For widely meeting the treatment demands of patients, it may be a better option to decrease the price or provide more patients with a financial assistance program for palbociclib both in the United States and in China. (*Clin Ther.* 2019;41:1175–1185) © 2019 Published by Elsevier Inc.

**Key words:** cost-effectiveness, metastatic breast cancer, palbociclib, second-line endocrine therapy.

## INTRODUCTION

Breast cancer is the most common cancer among US women and the second major cause of cancer-related death.[1] It was estimated that there were 246,660 women diagnosed with a history of invasive breast cancer and 40,450 deaths in the United States during 2016.[2] In China, the health burden of breast cancer

*Accepted for publication April 18, 2019*
https://doi.org/10.1016/j.clinthera.2019.04.033
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has significantly increased since the 1990s, with cases accounting for 12.2% of all newly diagnosed breast cancers and 9.6% of all deaths from breast cancer worldwide.[3] Moreover, the median age at the time of breast cancer diagnosis among Asians is nearly 10 years younger than in Western patients.[4] It places a heavy burden on patients and society. As far as we know, it eliminated the tariff on 28 categories of imported drugs in China from May 1, 2018. There are 103 preparations (e.g. azacitidine, carboplatin, and oxaliplatin) on the first batch of zero-tariff drugs list. We hope palbociclib will be imported with zero tariffs in the future.[5]

For hormone receptor−positive and human epidermal growth factor receptor 2−negative metastatic breast cancer ($HR^+/HER2^-$ MBC), endocrine therapy has become the mainstay of treatment.[6] Palbociclib, a highly selective inhibitor of cyclin-dependent kinases 4 and 6, has been approved as first- and second-line endocrine therapy for $HR^+/HER2^-$ MBC.[7,8] Recently, a subgroup analysis of data from the PALOMA-3 trial (Fulvestrant Plus Palbociclib Versus Fulvestrant Plus Placebo for Treatment of Hormone-Receptor-Positive, HER2-Negative Metastatic Breast Cancer That Progressed on Previous Endocrine Therapy) assessed the efficacy of palbociclib + fulvestrant (PAL + FUL) in Asians and non-Asians in the treatment of endocrine therapy−refractory MBC. In non-Asian patients, PAL + FUL demonstrated improved efficacy versus placebo (PCB) + FUL (median progression-free survival [PFS], 9.5 vs 3.8 months, respectively; hazard ratio = 0.451; 95% CI, 0.34−0.59; $P < 0.001$). Although the median PFS in Asian patients was not reached (9.2 months to not reached) in the palbociclib arm, the degree of PFS improvement in the PAL + FUL arm versus the PCB + FUL arm was similar to that in non-Asians (hazard ratio = 0.485; 95% CI, 0.27−0.87; $P = 0.0065$).[4]

Despite the substantial clinical benefit, as a new treatment option, palbociclib places a heavy financial burden on patients from the perspective of payers. Therefore, it is necessary to evaluate the cost-effectiveness of endocrine treatment in patients with MBC. Published studies have evaluated the economic outcomes of palbociclib in some developed countries (ie, the United States, Canada, and Switzerland), and suggested that the addition of palbociclib is not cost-effective.[9−11] However, the studies mentioned above provided economic information to the payers in developed countries. Our study paid direct attention to exploring the economy of new drugs and expensive drugs in both developing and developed countries. We expected that patients with MBC in developing countries could also get better treatment. This study explored the links and guides between developing and developed countries to provide the choices of new drugs. In this study, we assessed the cost-effectiveness of PAL + FUL as a second-line endocrine therapy for $HR^+/HER2^-$ MBC from the perspective of US and Chinese payers. Based on the analysis above, we identified the appropriate range of drug costs for which the addition of palbociclib to a fulvestrant therapeutic regimen could be considered cost-effective from a Chinese perspective.

## MATERIALS AND METHODS

### Analytical Overview and Model Structure

A Markov decision model was developed using R software (http://www.r-project.org) to simulate cancer progression and to predict the 10-year costs and survival benefits of the 2 strategic therapies. The model included 3 mutually exclusive health states: PFS, progression survival (PS), and death (Figure 1). In the Markov model, the cycle length was 4 weeks, which mirrored the treatment cycle length of the PALOMA-3 trial.[4] Patients began in the PFS state, and were randomly assigned to the treatment and comparison groups (PAL + FUL and PCB + FUL, respectively). According to the National Comprehensive Cancer Network guidelines, if there is disease progression after second-line therapy with PAL + FUL, there are no data to support an additional line of therapy with another regimen containing cyclin-dependent kinases 4 and 6.[12] After disease progression, we assumed that both groups received best supportive care until death.

The primary outputs were overall life-years gained, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs). We took 100,000 USD/QALY as the willingness-to-pay (WTP) threshold value in the United States.[13] In China, 26,840 and 58,480 USD/QALY were selected as the WTP threshold values for general regions and affluent regions, respectively.[14,15] Costs and outcomes were discounted at an annual rate of 3% for US payers,[16] and 5% for Chinese payers.[14] Costs in this

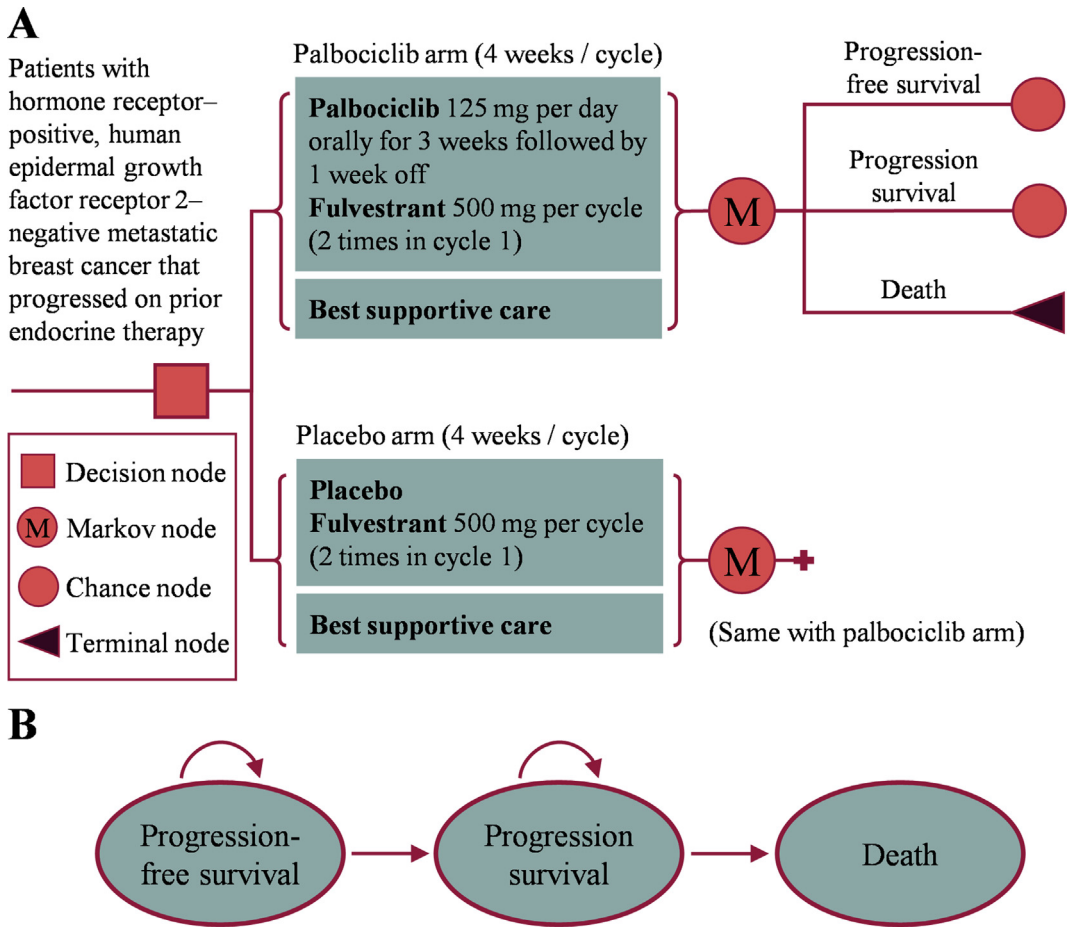


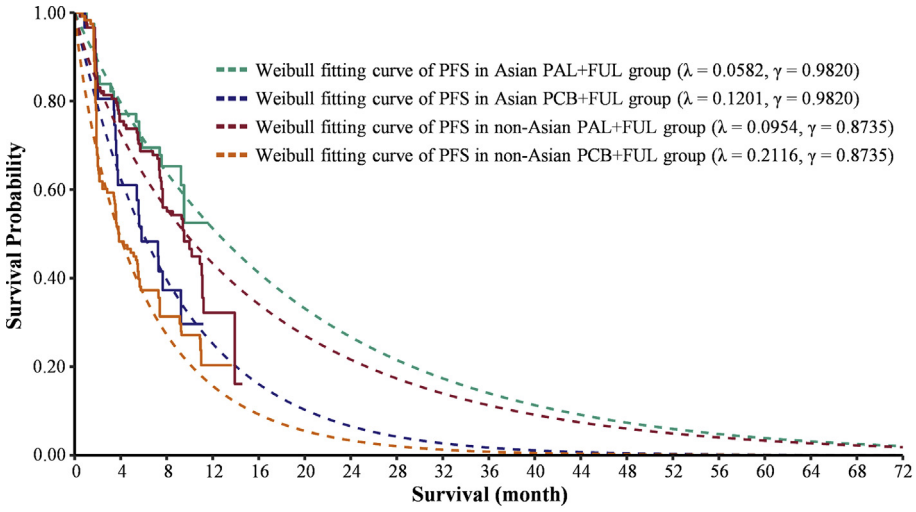

Figure 1. Markov decision tree (A) and Markov model structure (B) of drug regimens used to compare 2 treatment strategies for hormone receptor—positive, human epidermal growth factor receptor 2—negative metastatic breast cancer.

study were estimated in year-2018 USD with an exchange rate of 1 USD to 6.6174 Chinese yuan Renminbi (RMB).[17] One-way and probabilistic sensitivity analyses of parameters with ranges and distributions were performed to assess the stability of the model.

### Survival and Progression Risk Estimates

PFS data from the palbociclib arm and placebo arm in Asian and non-Asian groups were derived from the PALOMA-3 trial, and GetData Graph Digitizer software version 2.26 (http://getdata-graph-digitizer.com) was used to extract the PFS probabilities from the Kaplan—Meier curves of the trial.[4] We assumed that the PFS Kaplan—Meier curves could be fitted by Weibull proportional hazards models, in which the shape ($\gamma$) parameters of 2 groups (treatment group and comparison group) were the same, and the scale ($\lambda$) parameters of the treatment group were multiplied by those of the comparison group and the hazard ratio, that is, $\lambda_{TG}$ = Hazard ratio × $\lambda_{CG}$, where *TG* is the treatment group and *CG* is the comparison group. The results of the Weibull survival model for the comparison group are shown in Figure 2. The time-dependency transition of probabilities from the PFS to the PS state in each cycle was calculated according to the following formula:

$$tp(t_u) = 1 - \exp[\lambda(t-u)^{\gamma} - \lambda t^{\gamma}]\ (\lambda > 0;\ \gamma > 0), \quad (1)$$




| Group | Model | Clinical Data | Difference |
|---|---|---|---|
| Median PFS on Asian PCB + FUL group | 5.89 months | 5.8 months | 0.09 |
| Median PFS on Asian PAL + FUL group | 12.38 months | 9.2 to not reached | – |
| Median PFS on non-Asian PCB + FUL group | 3.89 months | 3.8 months | 0.09 |
| Median PFS on non-Asian PAL + FUL group | 9.67 months | 9.5 months | 0.17 |
| Median OS on Asian PCB + FUL group | 25.1 months | 25.1 months | 0.00 |
| Median OS on Asian PAL + FUL group | 33.78 months | not reported | – |
| Median OS on non-Asian PCB + FUL group | 25.1 months | 25.1 months | 0.00 |
| Median OS on non-Asian PAL + FUL group | 34.08 months | not reported | – |

Figure 2. The original Kaplan–Meier curves from the PALOMA-3 trial, Weibull fitting curves, and the validation of our model of treatment strategies for hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer. FUL = fulvestrant; OS = overall survival; PAL = palbociclib; PCB = placebo; PFS = progression-free survival.

where $u$ represents the Markov cycles and $t_u$ represents the arrival at state $t$ after $u$ Markov cycles.[18]

Due to a lack of available overall survival (OS) time in the PALOMA-3 trial, to minimize bias, we used the median OS time of 25.1 months, reported in a previous clinical trial of fulvestrant,[19] to calculate a constant mortality rate in the patients in the PS state:r = 1 – ln(1 – p)/t.[20] Then the calculated rates were adjusted to match the median OS. As a result, moralities of 0.03466 and 0.04058 per cycle were used for US and Chinese patients in our model inputs.

## Costs and Utilities

Medical costs of each strategy estimated from the perspective of the US and Chinese payers were based on data from the PALOMA-3 trial.[4] In our analysis, only direct medical costs were calculated in the model, including the costs of drugs, best supportive care (ie, administration, pain medications, monitoring, and minor adverse effects), the management of serious adverse events (SAEs) (grades 3 and 4), and routine follow-up. During the PALOMA-3 trial, patients underwent follow-up radiography, computed tomography, or MR imaging every 8 weeks for the first year and then every 12 weeks thereafter. Therefore, the unit cost of routine follow-up was added to the first cycle, 1 time per 2 model cycles in the first year and per 3 cycles thereafter. All costs were obtained from published literature and accessible sources and are presented in Table I.[4,12,21–26]

Table I. Costs and utilities of second-line endocrine therapy with palbociclib in $HR^+/HER2^-$ metastatic breast cancer.

| Parameter | US Value | | Chinese Value | | Basis of Distribution variables | |
|---|---|---|---|---|---|---|
| | Mean | Range | Mean | Range | | |
| Costs | | | | | | |
| Palbociclib, USD/mg | 5.162[21] | 3.613–6.711 | 1.716[22] | 1.201–2.231 | ±30% | γ |
| Fulvestrant, USD/mg | 3.917[12] | 2.742–5.092 | 3.561[23] | 2.493–4.629 | ±30% | γ |
| Follow-up, USD/unit | 1139[24] | 797–1481 | 166[23] | 116–216 | ±30% | γ |
| BSC, USD/cycle | 2933[24] | 2053–3813 | 807[23] | 565–1,049 | ±30% | γ |
| Neutropenia, USD | 9910[25] | 6937–12,883 | 701[26] | 491–911 | ±30% | γ |
| Anemia, USD | 13,679[25] | 9575–17,783 | 1030[26] | 721–1,339 | ±30% | γ |
| Risks for serious adverse events | | | | | | |
| Neutropenia in PAL + FUL group | 156/267 [58%][4] | 40.6%–75.4% | 67/73 [92%][4] | 64.4%–100% | ±30% | β |
| Anemia in PAL + FUL group | 8/267 [3%][4] | 2.1%–3.9% | 2/73 [3%][4] | 2.1%–3.9% | ±30% | β |
| Anemia in PCB + FUL group | 1/125 [0.7%][4] | 0.5%–0.9% | 2/29 [7%][4] | 4.9%–9.1% | ±30% | β |
| Neutropenia in PCB + FUL group | 1/125 [0.7%][4] | 0.5%–0.9% | 0/29 [0%][4] | – | ±30% | β |
| Utilities | | | | | | |
| Progression-free survival | 0.685[27] | 0.620–0.735[27] | 0.685[27] | 0.620–0.735[27] | 95%CI | β |
| Progression survival | 0.55[28] | 0.44–0.66 | 0.55[28] | 0.44–0.66 | ±20% | β |
| Hazard ratio of PFS | 0.451[4] | 0.343–0.593[4] | 0.485[4] | 0.270–0.869[4] | 95%CI | β |

BSC = best supportive care; FUL = fulvestrant; PAL = palbociclib; PCB = placebo; PFS = progression-free survival.

We considered the costs only of SAEs that occurred in >5% of patients and with a difference of >4% between the 2 groups in the PALOMA-3 trial. In this condition, the costs of neutropenia, leukopenia, and anemia were calculated in our analysis. According to expert consensus, the treatment of neutropenia covers that of leukopenia, so that the cost of leukopenia was not added to the total costs. We also calculated the expected costs of SAEs by summing the unit cost of each SAE multiplied its probability.

The utility values of the PFS and PS health states were obtained from the published literature and are listed in Table I.[27,28] The utility value of 0.685 (95% CI, 0.620–0.735) was used for all patients in the PFS state. The utility value of the PS state was derived from that in the literature, which was 0.55. Because the literature did not report the range of the utility for the PS state, we assumed ±20% as the high/low values (0.44–0.66).

## Sensitivity Analysis

One-way and probabilistic sensitivity analyses were performed to predict the uncertainty varied by parameter inputs in the simulation. Each key parameter was fitted with high/low ranges and various distributions in our model (Table I).[12,21–28] The ranges of costs and risks for SAEs were estimated by the base case with a variation of ±30%. Ranges of other parameters, except the utility of PS state (±20%), were obtained from the published literature. Probabilistic sensitivity analyses were conducted with a Monte Carlo simulation, in which parameters were sampled with a specific pattern of statistical distribution in 1000 iterations. γ Distributions were used for all input costs and β distributions for prevalence rates, utilities, and hazard ratios of PFS. The results of 1-way sensitivity analyses are depicted in a tornado diagram. Cost-effectiveness acceptability curves are

used to show the results of the probabilistic sensitivity analysis.

## RESULTS

### Validation of the Model

The 2-parametric Weibull proportional hazards models matched the PFS curves of the PALOMA-3 trial satisfactorily (Figure 2). Median PFS and OS times gained in our model were not significantly different from the findings of the PALOMA-3 trial[4] or the previous clinical trial of fulvestrant[19] (Figure 2). An iterative optimizing method, based on the least-squares method, was used to fit the PFS curves, and the constant mortality was calculated for a numerical simulation to fit the particular PFS data and the median OS time. The results were acceptable for validation of the model.

### Base-Case Analysis Results

Table II shows the results of the base-case analysis. Within a 10-year time horizon, the model predicted that the strategy of adding palbociclib yielded an additional 0.568 QALY at a cost of 488,854 USD/QALY in the United States. When palbociclib cost 30%, 20%, and 10% of the current price, the ICERs were 185,526, 142,193, and 98,860 USD/QALY, respectively. In China, the ICER was 182,779 USD/QALY. When palbociclib cost 30%, 20%, and 10% of the current price, the ICERs were 79,558, 64,812, and 50,066 USD/QALY, respectively.

### One-Way Sensitivity Analysis Results

Figure 3 provides tornado diagrams of the effect from uncertainty in parameter inputs on the base-case of ICER. From the US perspective, the results were sensitive to the price change of palbociclib. When the unit price of palbociclib was reduced to 70% of baseline (3.613 USD), the ICER fell to 358,856 USD/QALY. When the unit price of palbociclib was increased to 130% of baseline (6.711 USD), the ICER was changed to 618,851 USD/QALY. The other 2 most sensitive parameters included the hazard ratio of PFS (0.343–0.593, resulting in a range of ICER of 422,984–639,027 USD) and utility of PFS (0.62–0.735, resulting in a range of ICER of 539,551–455,902 USD), both of which were greater than the WTP threshold of 100,000 USD/QALY. Similarly, the most sensitive parameters in China (hazard ratio of PFS, unit price of palbociclib, and utility of PFS) resulted in ranges

Table II. Results of base-case analysis at 10-year horizon, of endocrine therapy with palbociclib in $HR^+/HER2^-$ metastatic breast cancer, from the US and Chinese perspectives.

| Treatment Strategy | Total Cost, USD | LYGs | QALYs | ICER, USD/LYG | ICER, USD/QALY |
|---|---|---|---|---|---|
| US perspective | | | | | |
| PCB + FUL | 123,280 | 2.900 | 1.672 | — | — |
| PAL + FUL | 400,784 | 3.730 | 2.240 | 334,062 | 488,854 |
| PAL at 30% cost + FUL | 228,596 | 3.730 | 2.240 | 126,780 | 185,526 |
| PAL at 20% cost + FUL | 203,998 | 3.730 | 2.240 | 97,169 | 142,193 |
| PAL at 10% cost + FUL | 179,400 | 3.730 | 2.240 | 67,557 | 98,860 |
| Chinese perspective | | | | | |
| PCB + FUL | 44,394 | 2.862 | 1.679 | — | — |
| PAL + FUL | 157,368 | 3.774 | 2.297 | 123,925 | 182,779 |
| PAL at 30% cost + FUL | 93,568 | 3.774 | 2.297 | 53,940 | 79,558 |
| PAL at 20% cost + FUL | 84,453 | 3.774 | 2.297 | 43,943 | 64,812 |
| PAL at 10% cost + FUL | 75,339 | 3.774 | 2.297 | 33,945 | 50,066 |

FUL = fulvestrant; ICER = incremental cost-effectiveness ratio; LYG = overall life-years gained; PAL = palbociclib; PCB = placebo; QALY = quality-adjusted life-years.

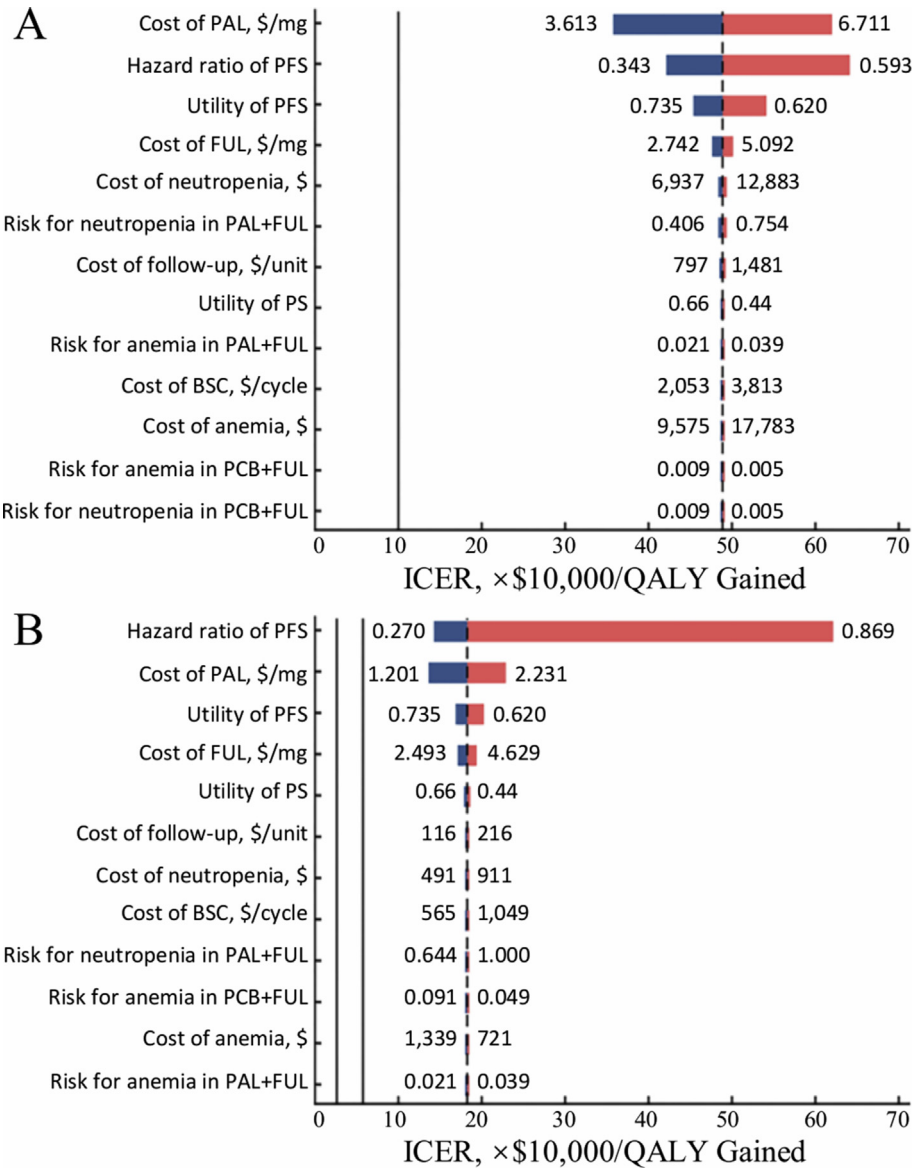



Figure 3. One-way sensitivity analysis of treatment strategies for hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer. Tornado diagrams showing uncertainty from model inputs of US (A) and Chinese (B) perspectives. The solid vertical lines represent the willingness to pay thresholds. The dotted vertical lines represent the base-case values. BSC = best supportive care; FUL = fulvestrant; ICER = incremental cost-effectiveness ratio; OS = overall survival; PAL = palbociclib; PCB = placebo; PFS = progression-free survival; PS = progression survival; QALY = quality-adjusted life-year.

of ICERs of 144,247 to 619,990, 138,541 to 227,017, and 201,056 to 170,834 USD/QALY, respectively, which were also greater than the Chinese thresholds of WTP (26,846 and 58,480 USD/QALY). All of the sensitive analyses indicated that our model was robust.

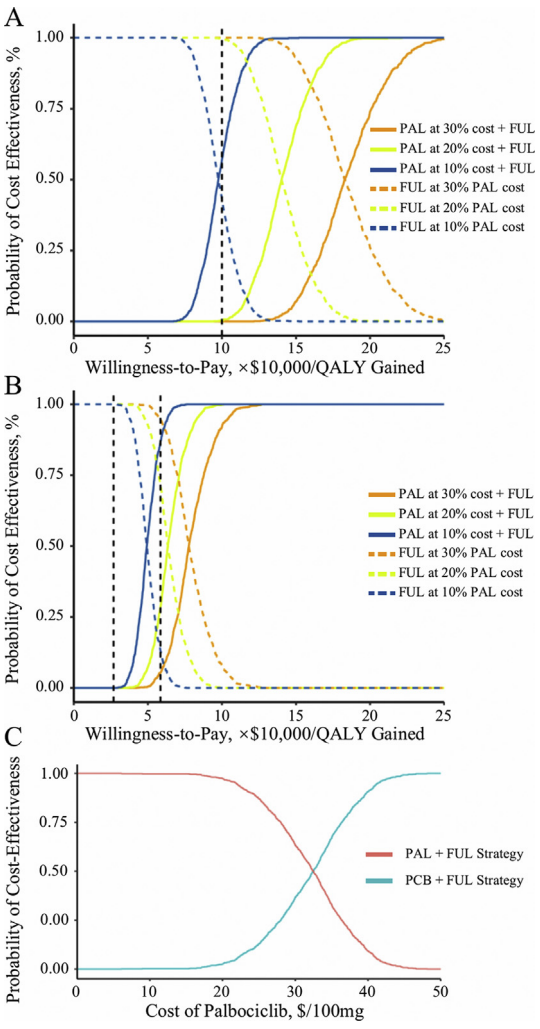



Figure 4. Probabilistic sensitivity analysis cost-effectiveness of treatment strategies for hormone receptor—positive, human epidermal growth factor receptor 2—negative metastatic breast cancer. Cost-effectiveness acceptable curves showing the cost-effective probability of palbociclib (PAL) + fulvestrant (FUL) at different prices from the US (A) and Chinese (B) perspectives. The dotted vertical lines represent the willingness to pay thresholds. C, Cost-effectiveness curves PAL + FUL and placebo (PCB) + FUL with different costs of palbociclib in Beijing. QALY = quality-adjusted life-year.

### Probabilistic Sensitivity Analysis Results

The results of probability sensitivity analysis showed that, in the United States, when the unit price of palbociclib was 30%, 20%, and 10% of the current price, the probabilities of cost-effectiveness in the treatment group were 0%, 0.4% and 57% respectively, at the WTP threshold of 100,000 USD/QALY (Figure 4). At the WTP threshold of 26,840 USD in China, each cost-effective probability in the treatment group was 0%. With the same strategy of price reduction, the cost-effective probabilities in the treatment group were 5.3%, 28.5%, and 86.8%, respectively, at the WTP threshold of 58,480 USD in Beijing (Figure 4). When the cost was reduced to 32.52 USD/100 mg in Beijing (an example in affluent regions), the probability of cost-effectiveness of adding palbociclib was increased to 50% (Figure 4).

## DISCUSSION

In this study, based on the latest reported data from the PALOMA-3 trial, we assessed the cost-effectiveness of adding palbociclib as a second-line endocrine therapy for HR$^+$/HER2$^-$ MBC from the perspectives of US and Chinese payers.

In the United States, the addition of palbociclib resulted in an ICER of 488,854 USD/QALY. A previous study of the cost-effectiveness of palbociclib in the United States concluded that the ICER of adding palbociclib in patients with prior endocrine therapy was 918,166 USD/QALY.[9] Although the ICER of PAL + FUL in our study was lower than that in the study by Mamiya et al,[9] we conclude that adding palbociclib is not cost-effective as a second-line endocrine therapy for MBC.

Our study is the first analysis to evaluate the health and economic outcomes of palbociclib as second-line treatment of patients with HR$^+$/HER2$^-$ MBC in China. This study might serve as a reference for further exploring the cost-effectiveness of palbociclib in developing countries in Asia.

One-way sensitivity analysis showed that the price of palbociclib had a significant impact on the ICER both in the United States and in China. Probability sensitivity analysis showed that even the if price of palbociclib were decreased by 90%, the probability of palbociclib being cost-effective in the general

regions was still 0%, which suggests that the PAL + FUL therapy provides poor value for the money as a second-line endocrine therapy for MBC in China. This finding may have been due to the following: (1) the medical costs in China were lower than those in the United States, but the incremental QALYs in Chinese patients were similar to those in US patients (the incremental QALYs were 0.568 and 0.618 in the United States and China, respectively); and (2) the WTP thresholds in China were much lower than that in the United States.

According to the Chinese guideline on pharmacoeconomic evaluations,[14] we used 3-fold the per-capita gross domestic product as the WTP threshold. Although the WTP threshold is lower than that in the United States, the results all revealed that adding palbociclib was not cost-effective for MBC. The sensitivity analysis suggested that when the cost was reduced to 32.52 USD/100 mg in Beijing (an example from affluent regions), the probability of cost-effectiveness of adding palbociclib would be increased to 50%. In China, there are 34 province-level administrative units, and in each province, the per-capita gross domestic product differs significantly. There are 4 province-level administrative units on the mainland (Tianjin, Shanghai, Jiangsu, and Zhejiang), the per-capita gross domestic product of which is similar to that of Beijing. Therefore, the price-reduction strategy attempt in Beijing could be applied to the 4 units on the mainland, and the 5 units together account for 14.3% of the population of China (197.44 million/1382.71 million).[15]

There were several potential limitations of this study. The first limitation is that the median OS time was derived from the previous clinical trial of fulvestrant,[19] instead of the PALOMA-3 trial, which might not have fit the OS curves accurately. However, this limitation cannot be avoided at present, because the median OS time in the PALOMA-3 trial has not been reported, and based on our literature search, there is no clinical trial that reports on a similar drug regimen or patient state. In our study, under the constant mortality of 0.04058 and 0.03466 in Asian and non-Asian patients, the median OS times in the treatment group were 33.78 and 34.08 months, respectively. In the PALOMA-1 trial,[29] the median OS with palbociclib + letrozole as a first-line of endocrine therapy was 37.5. In addition, the majority of the MBC patients are not cured, with a median OS of <3 years in many situations.[9] Hence, to some extent, the assumption could be considered reasonable and acceptable. The second limitation is about the utility values. In this study, the utility values were obtained from published literature and were assumed to be equal in the same health state, which may be different from the quality of life in patients in the PALOMA-3 trial. The third limitation is that our study considered the impact of only significant SAEs on costs, which may have led to calculated total costs lower than those in clinical practice.

Despite these limitations, the results of our simulation are justified. Our analysis was based on reasonable assumptions and adhered to the recommendations in Decision Modelling for Health Economic Evaluation[18] and the China Guidelines for Pharmacoeconomic Evaluations.[14] Nonetheless, the sensitivity analyses were carried out to assess the impact of uncertainty on the results.

## CONCLUSIONS

The addition of palbociclib to a regimen of fulvestrant is unlikely to be cost-effective as a second-line endocrine therapy for $HR^+/HER2^-$ MBC at the current price both in the United States and in China. For widely meeting the treatment demands of patients, it may be a better option to decrease the price or provide more patients with a financial assistance program for palbociclib.

## CONFLICTS OF INTEREST

This work was supported by the National Natural Science Foundation of China grants 81603081(C.Q.T.) and 81401547 (X.H.Z.) and the Key Science-Technology Research and Development Program of Hunan Province grant 20 16JC2062 (C.Q.T.). The funders had no role in study design, data collection and analysis, preparation of the manuscript or decision to publish. The authors have indicated that they have no conflicts of interest with regard to the content of this article.

## ACKNOWLEDGMENTS

Study design and supervision were contributed by C.Q. Tan and L.B. Peng. Data analysis and interpretation were contributed by Y.J. Zhang and X.H. Zeng.

Clinical program was contributed by F. Ma. Data collection was contributed by Y. Peng and L.D. Yi. Manuscript writing was contributed by Y.J. Zhang, X.H. Zeng, and H.J. Deng. All of the authors provided final approval of the manuscript. Y.J. Zhang and X.H. Zeng contributed equally to this work.

## REFERENCES


1. DeSantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A. Breast cancer statistics, 2017, racial disparity in mortality by state. *CA Cancer J Clin*. 2017;67:439–448.
2. Smith RA, Andrews K, Brooks D, et al. Cancer screening in the United States, 2016: a review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin*. 2016;66:96–114.
3. Fan L, Strasser-Weippl K, Li JJ, et al. Breast cancer in China. *Lancet Oncol*. 2014;15:e279–289.
4. Iwata H, Im SA, Masuda N, et al. PALOMA-3: phase III trial of fulvestrant with or without palbociclib in premenopausal and postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer that progressed on prior endocrine therapy-safety and efficacy in Asian patients. *J Glob Oncol*. 2017;3:289–303.
5. Zero tariffs on imported cancer drugs [China daily online]. Available at: http://usa.chinadaily.com.cn/a/201804/16/WS5ad3dafaa3105cdcf65185a2.html. Accessed February 24, 2019.
6. Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Ann Oncol*. 2014;25:1871–1888.
7. Beaver JA, Amiri-Kordestani L, Charlab R, et al. FDA approval: palbociclib for the treatment of postmenopausal patients with estrogen receptor-positive, HER2-negative metastatic breast cancer. *Clin Cancer Res*. 2015;21:4760–4766.
8. Walker AJ, Wedam S, Amiri-Kordestani L, et al. FDA approval of palbociclib in combination with fulvestrant for the treatment of hormone receptor-positive, HER2-negative metastatic breast cancer. *Clin Cancer Res*. 2016;22:4968–4972.
9. Mamiya H, Tahara RK, Tolaney SM, Choudhry NK, Najafzadeh M. Cost-effectiveness of palbociclib in hormone receptor-positive advanced breast cancer. *Ann Oncol*. 2017;28:1825–1831.
10. Raphael J, Helou J, Pritchard KI, Naimark DM. Palbociclib in hormone receptor positive advanced breast cancer: a cost-utility analysis. *Eur J Cancer*. 2017;85:146–154.
11. Matter-Walstra K, Ruhstaller T, Klingbiel D, Schwenkglenks M, Dedes KJ. Palbociclib as a first-line treatment in oestrogen receptor-positive, HER2-negative, advanced breast cancer not cost-effective with current pricing: a health economic analysis of the Swiss Group for Clinical Cancer Research (SAKK). *Breast Cancer Res Treat*. 2016;158:51–57.
12. 2018 ASP drug pricing files [centers for medicare and medicaid services website]. Available at: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles.html. Accessed February 24, 2019.
13. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med*. 2014;371:796–797.
14. Chinese Guidelines for Pharmacoeconomic Evaluations. *International society for pharmacoeconomics and outcomes Research website*; 2011. Available at: https://tools.ispor.org/PEguidelines/countrydet.asp?c=28&t=4. Accessed February 24, 2019.
15. National bureau of statistics of China [in Chinese]. Available at: http://data.stats.gov.cn/index.htm. Accessed February 24, 2019.
16. Siegel JE, Torrance GW, Russell LB, Luce BR, Weinstein MC, Gold MR. For the panel on cost effectiveness in health and medicine. Guidelines for pharmacoeconomic studies. Recommendations from the panel on cost effectiveness in health and medicine. *Pharmacoeconomics*. 1997;11:159–168.
17. Exchange rate [People's Bank of China website] [in Chinese]. Available at: http://www.pbc.gov.cn. Accessed February 24, 2019.
18. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*. New York: Oxford University Press Inc; 2006.
19. Di Leo A, Jerusalem G, Petruzelka L, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. *J Clin Oncol*. 2010;28:4594–4600.
20. Fleurence DRL, Hollenbeak CS. Rates and probabilities in economic modelling. *Pharmacoeconomics*. 2007;25:3–6.
21. DeMichele A. Present and future of CDK inhibitors. In: *Programs and Abstracts of the American Society of Clinical Oncology Annual Meeting*. June 1–5, 2018. Chicago, Ill.
22. Health Times in China [in Chinese]. Available at: http://www.jksb.com.cn/. Accessed February 24, 2019.
23. Ding H, Fang L, Xin W, Tong Y, Zhou Q, Huang P. Cost-effectiveness analysis of fulvestrant versus anastrozole as first-line treatment for hormone receptor-positive advanced breast cancer. *Eur J Cancer Care (Engl)*. 2017;26.

24. Sorensen SV, Goh JW, Pan F, et al. Incidence-based cost-of-illness model for metastatic breast cancer in the United States. *Int J Technol Assess Health Care*. 2012;28:12—21.
25. Rashid N, Koh HA, Baca HC, Lin KJ, Malecha SE, Masaquel A. Economic burden related to chemotherapy-related adverse events in patients with metastatic breast cancer in an integrated health care system. *Breast Cancer (Dove Med Press)*. 2016;8:173—181.
26. Dranitsaris G, Yu B, King J, Kaura S, Zhang A. Nab-paclitaxel, docetaxel, or solvent-based paclitaxel in metastatic breast cancer: a cost-utility analysis from a Chinese health care perspective. *Clinicoecon Outcomes Res*. 2015;7:249—256.
27. Lidgren M, Wilking N, Jonsson B, Rehnberg C. Health related quality of life in different states of breast cancer. *Qual Life Res*. 2007;16:1073—1081.
28. Sherrill B, Amonkar MM, Stein S, Walker M, Geyer C, Cameron D. Q-TWiST analysis of lapatinib combined with capecitabine for the treatment of metastatic breast cancer. *Br J Cancer*. 2008;99:711—715.
29. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol*. 2015;16:25—35.

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