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Cost-Utility of the CDK 4/6 Inhibitors for Postmenopausal Women With Luminal Advanced Breast Cancer in Brazil

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ABSTRACT

Objectives: Several trials have demonstrated the benefit of the CDK 4/6 inhibitors for postmenopausal women with luminal advanced breast cancer. This research aims to compare the cost-utility of the CDK 4/6 inhibitors in patients with no history of resistance to endocrine therapy.

Methods: A Markov model was constructed to estimate the incremental cost per quality-adjusted life-years (QALYs) of treatments from the Brazilian public health system perspective over a lifetime horizon (30 years) with 5% annual discount rate for both benefits and costs. Efficacy parameters were extracted from the pivotal studies. Costs were based on open data from the Brazilian Ministry of Health. The utilities were calculated according to the overall population preferences from a British study. Deterministic and probabilistic sensitivity analyses evaluated the robustness of the results.

Results: The most cost-effective drug was ribociclib (US$50 748/QALY), followed by abemaciclib (US$64 052/QALY) and palbociclib (US$65 289/QALY). The univariate analysis showed that the incremental cost-utility ratio (ICUR) was mainly sensitive to the overall survival hazard ratio. The one thousand–probabilistic simulation showed that all ICUR values were above classical thresholds such as 1 to 3 gross domestic product (GDP) per capita per QALY.

Conclusions: Even though there is no established willingness to pay threshold in Brazil, the estimated ICUR for CDK 4/6 inhibitors is >6 times the Brazilian GDP per capita (GDP per capita = US$5694.73), which might be a barrier to their inclusion in the Brazilian public health system.

Keywords: advanced breast cancer, CDK 4/6 inhibitors, cost-utility analysis, economic models.

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Introduction

Breast cancer (BC) is the leading type of cancer worldwide.[1] In Brazil, about the triennium of 2020 to 2022, 66 280 new cases are estimated, corresponding to a risk of 61.61 per 100 000 women and 29.7% of the total number of tumors diagnosed in that period.[2] The luminal histological subtype, that is, positive for hormone receptor and negative for human epidermal growth factor 2 (HER2−), represents 60% to 70% of the advanced BC cases.[3,4] Although different screening strategies have increased the diagnosis rate in the early stages, approximately 20% to 25% initially diagnosed in the early stages will have a metastatic recurrence, and 5% of patients already have metastatic BC at diagnosis.[5]

In the Brazilian public health system, known as *Sistema Único de Saúde* (SUS), healthcare is a constitutional right. The SUS covers varying health areas, such as health surveillance, research development, vaccination, emergency visits, hospitalizations, the supply of medicines, complementary examinations, and surgeries. There is a specific committee responsible for evaluating the inclusion of new technologies as an option in SUS and for elaborating clinical guidelines, the National Committee for Health Technology Incorporation into the Unified Health System (*Comissão Nacional de Incorporação de Tecnologia no SUS*—Conitec).[6]

The Brazilian clinical guidelines recommend hormone therapy as the first-line therapy for postmenopausal women with advanced luminal BC.[7] In contrast, international guidelines recommend adding CDK 4/6 inhibitors (abemaciclib, palbociclib, or ribociclib) in the first-line therapy.[5] Pivotal studies demonstrated an increase in overall survival (OS) and progression-free survival (PFS) using CDK 4/6 inhibitors in advanced luminal BC.[3,8-13]

Although the availability of new effective therapeutic options for BC treatment may be beneficial, the limited financial resources available in the Brazilian public health system may represent an obstacle to the incorporation of CDK 4/6 inhibitors. Therefore, this research aims to evaluate the cost-utility of CDK 4/6 inhibitors as first-line therapy for postmenopausal women with advanced luminal BC, from the perspective of the Brazilian public health system.

Methods

Rapid Review

We conducted a rapid review in the MEDLINE, Embase, and LILACS databases to retrieve systematic reviews and network meta-analysis (NMA) regarding the efficacy of CDK 4/6 inhibitors as first-line therapy in postmenopausal women with advanced luminal BC who had not received previous systemic therapy for advanced disease. Search terms included "breast" or "mammary" and disease descriptors ("cancer," "neoplasm," or "tumor") and "metastasis" and "advanced." Search terms for treatments included "palbociclib," "ribociclib," and "abemaciclib." Exclusion criteria were unavailable full texts and languages other than English, Portuguese, and Spanish. All searches were last updated in June 2020. To assess the risk of bias of original studies, we used the Cochrane Collaboration Tool.[14]

Model Design

Data from randomized clinical trials[3,8-11] and NMAs[15] evaluating the efficacy and safety of the CDK 4/6 inhibitors were used in a health-state transition. Markov model with monthly cycles was used to estimate the cost-utility of CDK 4/6 inhibitors when added to the endocrine therapy in women with advanced luminal BC. The Brazilian public health system perspective, over a lifetime horizon, with a 5% annual discount rate for both costs and effectiveness was considered.

The model was developed in Microsoft Excel®[16] with 3 mutually exclusive disease states: PFS, postprogression survival (PPS), and death as the absorbing health state (Fig. 1). The cohort was assumed to start in the PFS state, and during each cycle, patients could remain in PFS, transit to PPS, or transit to death. In the PPS state, patients could remain in PPS or transit to death.

The survival curves referent to the endocrine therapy in the MONALEESA-2 and MONALEESA-7 trials were used as the baseline risks for patients progressing to PPS and death, respectively. These trials were selected to reflect the baseline risks because they had a greater number of patients and a longer period of follow-up than other CDK 4/6 inhibitors trials.

The proportion of PFS events that resulted in death was estimated using original MONALEESA-7 data, with the assumption that it was dependent on the initial treatment received (endocrine therapy or CDK inhibitors) but independent of the type of CDK inhibitor. To estimate the percent of events from the PFS state that were disease progression, we discounted the percent of deaths from the percent of events observed in MONALEESA-2, so that every event that was not a death was considered disease progression.

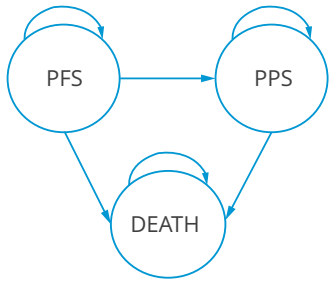
Data were extracted from MONALEESA-2 and 7 using WebPlotDigitizer®[17] with extrapolations of survival data generated in Excel 2010.[16] The selection of the most appropriate extrapolation method among Weibull, log-logistic, exponential, Gompertz, and lognormal was based on the visual and on the Akaike information criteria (see Appendix Tables 3 and 4 in Supplemental Materials found at https://dx.doi.org/10.1016/j.vhri.2022.02.006), with the Weibull distribution being the best fit both for disease progression and OS (Appendix Figs. 1 and 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.02.006). The original data observed in the Kaplan-Meier curve itself were considered for short-term survival supplemented with Weibull extrapolation used only for long-term survival.

Efficacy

The efficacy was modeled considering the results from an NMA using the Bayesian hierarchical arm-based model.[15] All the CDK 4/6 inhibitors were associated with a substantially longer PFS than endocrine monotherapy. In the indirect comparison across the 3 classes of CDK 4/6 inhibitors, the hazard ratios (HRs) calculated were 0.63 (95% confidence interval [CI] 0.47-0.86) for abemaciclib, 0.68 (95% CI 0.53-0.87) for palbociclib, and 0.65 (95% CI 0.53-0.79) for ribociclib. These HR values were used in the model to estimate the hazard reduction to transit from PFS to PPS.

For OS, the studies data are immature. Recently, data on OS have been reported in the MONALEESA-7 study where the estimated OS at 42 months was 70.2% (95% CI 63.5-76.0) in the CDK 4/6 inhibitor arm (ribociclib) versus 46% (95% CI 32-58.9) in the endocrine monotherapy arm.[11] Data from the MONALEESA-7 were used (HR 0.71; 95% CI 0.54-0.95) as the hazard reduction to transit from PFS/PPS to death. Given that there is no proof of superiority in the efficacy of either of the CDK 4/6 inhibitors, the same HR for OS was considered regardless of treatment. Finally, given that there are no data to distinguish the mortality rate between groups with and without disease progression, we conservatively used the assumption that the probability of transitioning to death in the PFS and PPS states would be the same.

Figure 1. Markov cycle states.



PFS indicates progression-free survival; PPS, postprogression survival.

Assumptions

The model assumed that after transiting to PPS the treatment is changed to chemotherapy, which is maintained for the patient's lifetime. In addition, transitioning to the PPS state was associated with new metastasis, with site-specific data derived from a retrospective study of metastasis in patients with advanced luminal BC.[18]

Utility Parameters

The utilities of each health state were estimated based on a British study[19] that is considered to be the largest preference study in BC. Different utilities were estimated for each CDK 4/6 inhibitor according to the frequency of side effects.[3,8-10] The percents of side effects for abemaciclib, palbociclib, and ribociclib were 1.3%, 1.8%, and 1.5% for febrile neutropenia; 14.3%, 1.9%, and 4.8% for diarrhea/vomiting; 0.5%, 0.2%, and 0.0% for stomatitis; and 2.7%, 2.3%, and 2.4% for fatigue, respectively. The utilities in PFS/PPS states were calculated to be 0.778/0.527 for abemaciclib, 0.788/0.541 for palbociclib, 0.786/0.539 for ribociclib, and 0.793/0.548 for endocrine therapy.

Cost Parameters

Specific monthly costs for each CDK 4/6 inhibitor (abemaciclib US$2401.19; palbociclib US$2511.78; ribociclib US$1932.95) were estimated based on *Banco de Preço em Saúde* (Health Price Bank),[20] an official database that presents the values paid by the public hospitals in their latest purchases. It was also considered that the percent of dose reduction and side effects observed in the pivotal trials and the costs were adjusted accordingly.

Table 1. Parameters used in the model and the limits used in sensitivity analysis.

Parameter	Mean	Lower	Higher	Distribution	Source
Endocrine monotherapy PFS costs	$129.76	$103.81	$155.71	Gamma	21
Abemaciclib PFS costs	$2534.73	$2027.78	$3041.68	Gamma	20
palbociclib PFS costs	$2645.32	$2116.26	$3174.38	Gamma	20
Ribociclib PFS costs	$2066.49	$1653.19	$2479.79	Gamma	20
PPS costs	$633.85	$507.08	$760.62	Gamma	21
Costs of death	$212.91	$170.33	$255.50	Gamma	21
Utilities of endocrine therapy PFS	0.793	0.641	0.891	Beta	19
Utilities of ribociclib PFS	0.786	0.636	0.887	Beta	19
Utilities od endocrine therapy PPS	0.539	0.404	0.691	Beta	19
HR PFS to PPS (abemaciclib)	0.63	0.47	0.86	Lognormal	10
HR PFS to PPS (palbociclib)	0.68	0.53	0.87	Lognormal	3
HR PFS to PPS (ribociclib)	0.65	0.53	0.79	Lognormal	9
HR ribociclib PFS/PPS to death	0.710	0.540	0.950	Lognormal	11
Annual costs discount rate	5.00%	0.00%	10.00%	Beta	22
Annual efficacy discount rate	5.00%	0.00%	10.00%	Beta	22

HR indicates hazard ratio; PFS, progression-free survival; PPS, postprogression survival.

Costs were subdivided according to Markov states and were extracted from official and open Brazilian government databases.[21] The costs of the PFS and PPS states were based on the number of outpatient appointments, complementary examination, and drug costs. The frequency of patient monitoring (outpatient appointments and complementary examinations) in each health state, besides the pattern of health resources, was based on a guideline proposed by the Brazilian Ministry of Health.[7] The health resources were split into 2 groups depending on whether or not CDK 4/6 inhibitors were used. A greater necessity of monitoring was assumed in the CDK 4/6 inhibitors arm than the endocrine monotherapy (Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.02.006).

The cost of the PPS state also included the treatment of metastases (Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.02.006), which was calculated based on the affected location. The estimate of the percent of the metastasis site was extracted from the subgroup of patients with luminal BC from a database with information from 159 344 women with BC.[18] The most common site of metastases was the bone (79.7%), followed by the lung (11%), the liver (8.1%), and the brain (1.2%). Radiotherapy (US$46.48), pain relievers (US$1.89), osteolysis inhibitors (US$80.4), and surgery (US$73.39) were all included in the costs of a bone metastasis case. Only the costs of radiotherapy were included in the costs of pulmonary and cerebral metastasis (US$53.12 and US$75.06, respectively). Hepatic metastasis had no additional costs.

Finally, death costs were estimated by the average value of hospital admissions of patients with BC who evolved to death. All costs were converted from reais to dollars, with an exchange rate equivalent to R$5.59 = US$1.00, and updated on September 30, 2020. Brazilian oncologists validated the necessity of all health resources and the average frequency.

One-Way Sensitivity Analyses

A deterministic model was constructed for each CDK 4/6 inhibitor examining the impact of changing the value of one parameter at a time on the incremental cost-utility ratio (ICUR). The range of each parameter and its distribution are presented in Table 1.[3,9–11,19–22] The utilities and HRs varied among 95% CI limits, whereas unit costs varied by ±20%. The discount rate varied between 0% and 10%. The tornado diagram depicted the outcomes of the one-way sensitivity analyses.

Probabilistic Analyses

The primary outcome was ICUR, calculated as the difference in costs for each CDK 4/6 inhibitor versus endocrine therapy alone divided by the difference in quality-adjusted life-years (QALYs). The probabilistic analysis was conducted using 1000 iterations from random draws of the underlying parameter uncertainty (showed in Table 1[3,9–11,19–22]) and expressed as ICUR scatter plots and cost-effectiveness acceptability curves for each CDK 4/6 inhibitor.

Table 2. Cost-effectiveness between endocrine monotherapy and CDK 4/6 inhibitors for women with advanced luminal breast cancer.

Treatments/outcomes	Costs (US$)	YPFS	LY	QALYs	ICUR (US$)
Endocrine monotherapy	14 766.50	0.60	2.40	1.41	—
Endocrine plus abemaciclib	63 276.05	1.67	3.28	2.15	64 052.78
Endocrine plus palbociclib	64 377.78	1.63	3.28	2.18	65 289.41
Endocrine plus ribociclib	53 49.37	1.65	3.28	2.18	50 748.64

ICUR indicates incremental cost-utility ratio; LY, life-years; QALY, quality-adjusted life-year; YPFS, years of progression-free survival.

Results

All the CDK 4/6 inhibitors were found to be more effective and costly than endocrine therapy alone. Among the CDK 4/6 inhibitors, the most cost-effective was ribociclib, with a cost of $53 549.37, a QALY of 2.18, and an ICUR of $50 748.64. The second most cost-effective drug was abemaciclib with a cost of $63 276.05, a QALY of 2.15, and an ICUR of $64 052.78 and, finally, palbociclib with a cost of $64 377.78, a QALY of 2.18, and an ICUR of $65 289.41 (Table 2).

The univariate analysis showed that the ICUR value was sensitive to some parameters, mainly the HR for OS, the utilities values, and the cost of the intervention, consistently showing values above US$59 000 per QALY. The results of the univariate analysis of ribociclib are presented in a tornado graph shown in Figure 2, whereas the results of abemaciclib and palbociclib are shown in Appendix Figure 3A, B in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.02.006, respectively.

The results of the probabilistic analysis are presented in a scatter plot in Figure 3. Most results are in the right upper quadrant, indicating that the CDK 4/6 inhibitors generated a greater gain in QALYs at a higher cost. There is a significant overlap of the results in the probabilistic analysis, although it is possible to observe that the most cost-effective drug among the 3 CDK 4/6 inhibitors is ribociclib.

The acceptability curve shows the results of the probabilistic model representing the point from which the technology is most likely to be cost-effective. The CDK 4/6 inhibitor is more likely to be cost-effective (>50%) if the willingness to pay per QALY is >US$63 500 for abemaciclib, US$66 400 for palbociclib, and US$50 750 for ribociclib (Fig. 4).

Discussion

To the best of our knowledge, there is no evidence regarding BC patients' preferences, prognosis, or cost-utility analysis of CDK 4/6 inhibitors from the perspective of the Brazilian public health system. The current evidence consistently demonstrates an increase of at least 10 months in PFS with the addition of CDK 4/6 inhibitors to endocrine therapy in patients with advanced luminal BC. Although some authors question the relevance of this outcome, patients who remain in the PFS state may postpone chemotherapy, which may be valued by many patients.[23,24] According to a recent survey that sought to rank the outcomes valued by cancer patients and carers,[25] survival and progression were the 2 most important outcomes. Besides that, new data from 2 studies have shown that the CDK 4/6 inhibitors also improve OS in this population.[11,26] It is worth mentioning that, only in 2019, the Brazilian Mortality Information System recorded 18 296 deaths in women due to BC, the principal cause of death from cancer in Brazilian women. Data from 1980 to 2006 showed that BC mortality has been increased in all 5 major geographic regions of Brazil.[27]

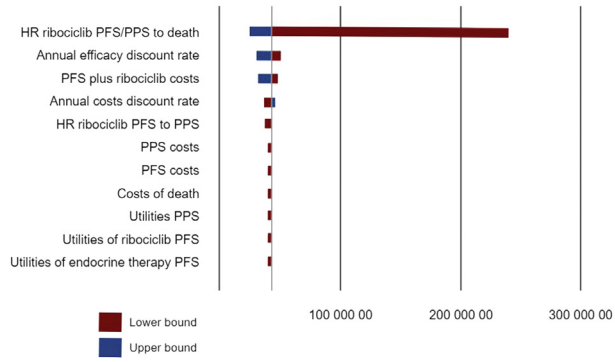
The CDK 4/6 inhibitors, recently assessed and included in the National Agency of Supplementary Health, could benefit Brazilian patients who exclusively rely on the public health system as therapeutical alternatives that can favor management and individualization according to the patient's tolerability profile.

Nevertheless, despite the documented benefits concerning clinical profile, there are no head-to-head studies, and the indirect comparisons about PFS did not identify the superiority of any drug.[15] Hence, based on the similar clinical profile of all the CDK 4/6 inhibitors, their economic impact may be the decisive criterion in the decision making of which if any of them should be incorporated into the Brazilian public health system.

Even though there is no set threshold for incorporating technologies in Brazil, the ICURs identified might be considered above the Brazilian Ministry of Health's willingness to pay. Considering as a reference, one Brazilian gross domestic product (GDP) per capita (US$5694.73), all technologies presented an ICUR far higher than 6 times the GDP per capita/QALY.[28]

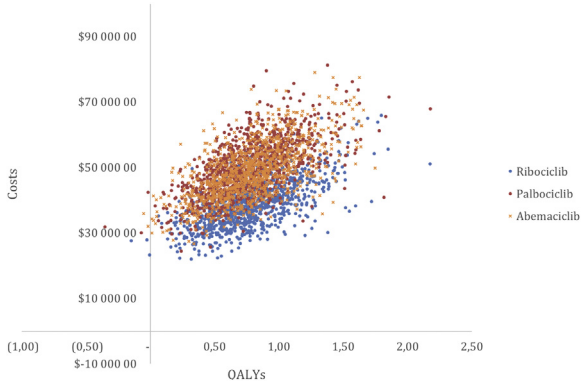
There are limitations in this study. Regarding the efficacy of CDK inhibitors, the model assumed the same risk of death regardless of the drug, which should be highlighted as a conservative approach, mainly because palbociclib has 2 independent studies (PALOMA-1 and PALOMA-2) that show negative results for OS. Besides that, because clinical trials reporting PFS and OS are scarce and have a small follow-up, it was necessary to extrapolate the data, which increases the uncertainty regarding the results. Despite this, we used a systematic method based on a priori determined selection criteria (Akaike information criteria) to provide a transparent approach and to reduce the risk of bias. Furthermore, given the high ICUR values, it is highly unlikely that any method of data analysis will render the CDK 4/6 inhibitors

Figure 2. One-way sensitivity analysis ICUR for the ribociclib in combination with endocrine therapy versus endocrine therapy alone for women with advanced luminal breast cancer.



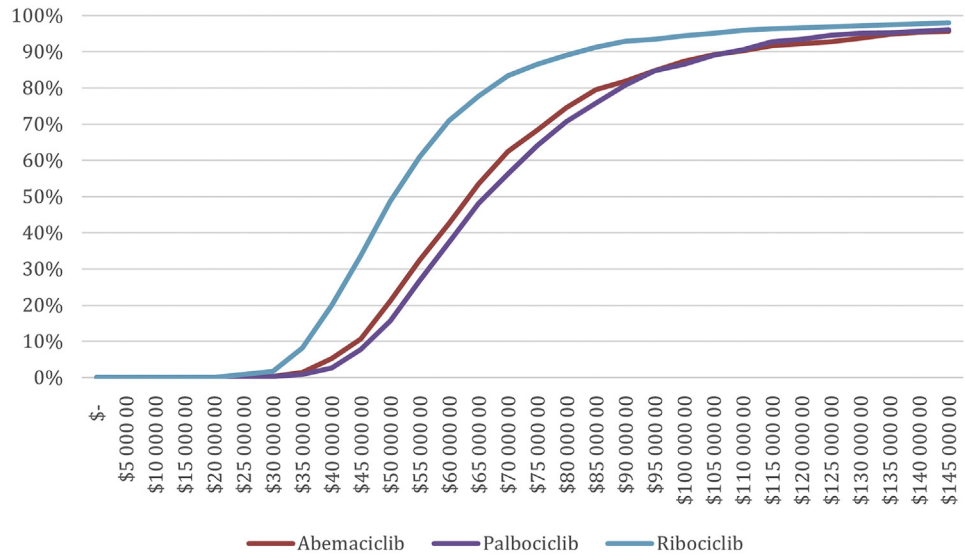
HR indicates hazard ratio; ICUR, incremental cost-utility ratio, PFS, progression-free survival; PPS, postprogression survival.

Figure 3. Cost-utility scatter plot for the CDK 4/6 inhibitors in combination with endocrine therapy versus endocrine therapy alone for women with advanced luminal breast cancer.



QALY indicates quality-adjusted life-year.

Figure 4. ICUR acceptability curve for the CDK 4/6 inhibitors in combination with endocrine therapy versus endocrine therapy alone for women with advanced luminal breast cancer.



ICUR indicates incremental cost-utility ratio.

cost-effective at traditional thresholds such as one to 3 GDP per capita per QALY. The mixing of PFS and OS from 2 separate trials (MONALEESA-2 and MONALEESA-7) relies on the assumption that the 2 sources are generalizable to each other, which may not be true. Despite the fact that the utility values were derived from the largest preference study in BC, their generalization to the Brazilian patient population was not validated. Finally, the use of public reimbursement data may have resulted in an underestimation of costs, which could affect the model's performance.

Conclusions

In terms of PFS and OS, CDK 4/6 inhibitors combined with endocrine therapy outperformed endocrine monotherapy. Head-to-head comparisons of CDK inhibitors could aid in determining any differences between abemaciclib, palbociclib, and ribociclib. For the time being, evidence suggests that all CDK 4/6 inhibitors have comparable safety and efficacy profiles, based on PFS outcome, with the cost being the most important consideration. Ribociclib was the most cost-effective drug; nevertheless, the estimated ICUR is >6 times the Brazilian GDP per capita, making its implementation into the Brazilian public health system economically challenging.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://dx.doi.org/10.1016/j.vhri.2022.02.006.

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Drafting of the manuscript: Schroeder Macedo, Magliano, Santos
Critical revision of the paper for important intellectual content: Schroeder Macedo, Silveira Silva, França, Magliano, Meirelles, Piccin Padilla, Santos
Statistical analysis: Magliano
Administrative, technical, or logistic support: Schroeder Macedo, Magliano, Santos
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