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Cost-effectiveness of ribociclib plus letrozole *versus* palbociclib plus letrozole or letrozole as monotherapy in first-line treatment of postmenopausal women with HR+/HER2– locally advanced or metastatic breast cancer: a Brazilian private payer perspective

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Abstract

Background: The global burden of breast cancer (BC) is high, especially in advanced stages. CDK 4/6 inhibitors represent a paradigm shift in the treatment of advanced BC HR+/HER2–, given the clinically and statistically significant gain in overall survival associated with this new class of medications. Nevertheless, as an innovation, the incorporation of these drugs impacts healthcare budgets, requiring cost-effectiveness analyses for decision-making. The aim of this study was to evaluate the cost-effectiveness of ribociclib plus letrozole compared with palbociclib plus letrozole or letrozole as monotherapy for first-line treatment of postmenopausal women with HR+/HER2– locally advanced or metastatic BC (aBC) from a Brazilian private healthcare system perspective.

Methods: A model including progression-free survival (PFS), progressed disease, and death health states was used to simulate lifetime costs and outcomes. PFS and overall survival were derived from the MONALEESA-2 trial (lifetime horizon). Healthcare costs included drug acquisition and monitoring, subsequent therapies, adverse events, and end-of-life costs. Effectiveness was measured in quality-adjusted life-years (QALYs). Deterministic and probabilistic sensitivity analyses were performed.

Results: The total cost of treatment with ribociclib plus letrozole was USD 72,091.82 *versus* USD 92,749.64 for palbociclib plus letrozole. Total QALYs were 3.30 and 3.16, respectively. Base-case analysis showed ribociclib as dominant over palbociclib in first-line treatment of women with HR+/HER2– aBC, associated with cost savings and QALY gains. The total cost of treatment with ribociclib plus letrozole was USD 83,058.73 *versus* USD 29,215.10 for letrozole. Total QALYs were 3.84 and 2.61, respectively. Compared with letrozole, ribociclib plus letrozole was associated with an incremental cost of USD 53,843.64 and an incremental QALY gain of 1.23, with incremental cost-effectiveness ratio of USD 43,826.91 per QALY gained.

Conclusions: As demonstrated by the cost-effectiveness dominance over palbociclib, ribociclib results in savings when used as first-line treatment in postmenopausal women with HR+/HER2– aBC, warranting incorporation in the private healthcare system.

Keywords: breast cancer, CDK 4/6 inhibitors, cost-effectiveness study, health technology assessment, ribociclib

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Introduction

Breast cancer (BC) is the most incident type of cancer among Brazilian women, with an estimated 66,280 new cases in 2020.[1] BC subtypes expressing the estrogen receptor or progesterone receptor [hormone receptor-positive (HR+)] account for up to 75% of the cases.[2,3] Despite treatment advances in BC, approximately 30% of women with early disease will eventually suffer a recurrence and develop locally advanced or metastatic BC (aBC) during their lives.[4] Until recently, endocrine therapies (ETs) were considered the standard of care for postmenopausal women with aBC;[5,6] however, despite a satisfactory effectiveness of first-line ETs, primary or developed resistance occur in most patients, with additional lines of ET providing very little clinical benefit.[7] In this regard, for first-line therapy with letrozol, we can expect progression-free survival (PFS) estimates ranging from 9.4 to 16 months.[8,9] In second-line therapy, these estimates drop to 5.6 months.[10] For anastrozol, PFS with first-line therapy is estimated to range from 13.1 to 13.8 months,[11,12] dropping to 5 months with second-line therapy.[10] For fulvestrant, PFS ranges from 23.4 to 16.6 months with first-line therapy,[11,12] dropping to 4.8 months with second-line therapy.[13]

Endocrine resistance is a serious clinical problem resulting from estrogen receptor gene (*ESR*) alterations (mutations, amplifications, or translocations) and/or upregulation of alternative pathways, such as the HER2 growth factor pathways and the PI3K/AKT/mTOR pathway. Targeted therapies that act on pathways of endocrine resistance improve PFS in combination with standard hormone agents, and emerge as an important treatment option in the presence of ET resistance.[14] Other alternatives impacting replication mechanisms, such as cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors have also emerged to overcome endocrine resistance, after initial US Food and Drug Administration approval in 2016.

The three types of CDK 4/6 inhibitors that are currently available, ribociclib, abemaciclib and palbociclib, have different pharmacological properties but share the same mechanism of action, inhibiting CDK4/6 that blocks the phosphorylation of retinoblastoma protein, thus preventing cell-cycle progression and inducing G1 phase arrest.[15] This process results in reduced cell viability and tumor response.

CDK 4/6 inhibitors have been studied in several phase III pivotal randomized controlled trials (RCTs), with ribociclib (LEE011) having the largest body of evidence, represented by the MONALEESA clinical program. In this program, ribociclib was studied in association with aromatase inhibitors (AIs)[9,15,16] or fulvestrant[17] in first[9,15–17] and second[17] lines of treatment in pre/peri[16] and postmenopausal women[9,15,17] with ER+/HER2− aBC. In the three landmark RCTs (MONALEESA-2,[9,15] MONALEESA-3,[17] and MONALEESA-7[16]), ribociclib plus ET resulted in significant improvement in PFS, overall response rate, and net clinical benefit when compared with ET plus placebo. The combined use of ribociclib and ET was also able to maintain[17,18] or improve[16] patient quality of life. Recently published MONALEESA-7[19] and MONALEESA-3[20] results have shown consistent and significant improvement in overall survival (OS) in pre, peri, and postmenopausal women with ER+/HER2− aBC, regardless of combination partner (i.e. AI or fulvestrant) or line of treatment. In this sense, in the MONALEESA-7 trial, the use of ribociclib in association with ET was able to reduce the risk of death by 29% compared with ET monotherapy plus placebo in the first-line treatment of peri/premenopausal women with aBC.[19] In MONALEESA-3, ribociclib in association with fulvestrant was able to reduce the risk of death by 28% compared with fulvestrant monotherapy plus placebo in first and second lines treatment of postmenopausal women with aBC.[20]

Palbociclib and abemaciclib have also demonstrated superiority in terms of PFS and response rates when compared to monotherapy with either drug.[21–24] However, palbociclib did not demonstrate statistical OS benefits when associated with fulvestrant in postmenopausal women.[25] Abemaciclib demonstrated significant OS only in second-line therapy or in ET-resistant patients (early relapses).[26] Further, palbociclib and abemaciclib have not been studied in exclusively pre/perimenopausal populations or in combination with fulvestrant in patients with *de novo* diagnosis or endocrine sensitivity in first-line treatment. In this sense, populations differ significantly across trials, which could compromise the comparability of molecules for the entire range of patient profiles studied.

One exception is the association of CDK4/6 inhibitors and letrozole in postmenopausal women with ER+/HER2− aBC who were sensitive to ET

(defined as patients relapsing ⩾12 months of previous adjuvant therapy or with *de novo* diagnosis of aBC). This population was studied in the MONALEESA-2,[9,15] PALOMA-1,[27] PALOMA-2,[22] and MONARCH-3[23] trials. All trials report similarities in PFS efficacy; mortality data in all phase 3 trials, however, remains immature to demonstrate differences in OS.

While representing a shift in paradigm for the treatment of HR+/HER2− aBC such innovations need to be evaluated from an economic perspective. BC is a highly prevalent and incident disease, and therefore an increase in treatment costs resulting from the incorporation of these health technologies could significantly impact health care budgets, especially in low- and middle-income countries. In this sense, cost-effectiveness analyses are essential for health technology assessment and decision-making regarding reimbursement of innovative therapies in many countries, including Brazil. Therefore, this study was designed to evaluate the cost-effectiveness of ribociclib plus letrozole compared with palbociclib plus letrozole or letrozole as monotherapy for the first-line treatment of postmenopausal women with HR+/HER2− aBC from the perspective of the Brazilian private healthcare system.

Methods

Model structure

A cohort-based partitioned survival model was developed in Microsoft Excel to estimate costs and quality-adjusted life-years (QALYs) associated with ribociclib plus letrozole as compared with palbociclib plus letrozole and letrozole monotherapy from the Brazilian third-party payer perspective. Institutional ethics committee approval was not required given the study design (mathematical model).

The model comprised three health states: progression-free (PF), progressed disease (PD), and death (Figure 1). PF was further partitioned into two substates corresponding to PF with objective response (complete or partial) and PF with stable disease, used to generate treatment-specific and response-average utility weights within the PF state. In line with data from MONALEESA-2, the number of patients reaching the PF with response state was assumed to increase linearly over the first 12 months; after that, the probability of progression estimated from the PFS curve was

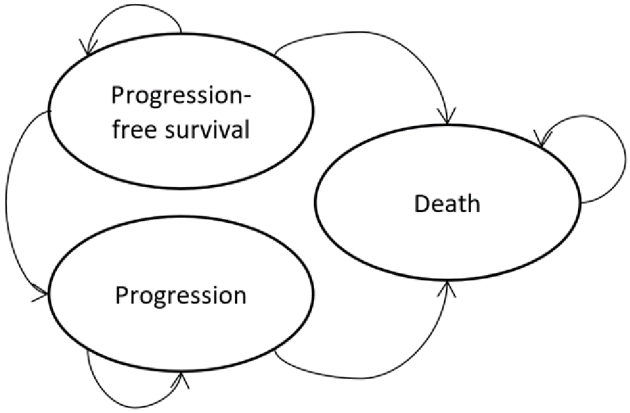

Figure 1. Health state structure for the economic model.

applied to the numbers occupying the PF with response state, to account for progression in the responder population. Occupancy for the PF with stable disease state was estimated as the difference in the numbers occupying the PF and the PF with response states. The transitions between the states were directly estimated based on the area under the curves for PFS and OS, defining state occupancy over time. The proportion of alive or PD patients was estimated based on the difference between OS and PFS curves.

The cohort in the model was initially assigned to the PF with stable disease state. From that state, patients can enter one of the PF with response substates, PD, or death. Response to therapy was defined by the RECIST criteria (version 1.1).[28] Transition from PF with stable disease to PF with response was assumed to entail improvement in quality of life, based on data from the MONALEESA-2[18] trial and the literature. Transition from PF to PD was assumed to result in declining quality of life because of disease progression. The PD state was assumed to capture the clinical outcomes after later lines of treatment. Once patients enter in PD, the cohort can only transition to the death state, the absorbing state, with patients assuming to occupy this state indefinitely.

The total costs and effectiveness of treatment are estimated by combining the numbers of patients occupying each health state over time, with the costs and health utilities assigned to each state. State occupancy was modelled at monthly intervals (365.25/12 days) over the course of a modelled time horizon of up to 40 years (lifetime). A monthly cycle (30.44 days) was chosen based on the ribociclib and palbociclib cycles in first-line

Table 1. Estimates of efficacy used in the model.

Survival	Ribociclib + letrozole	Letrozole monotherapy	Palbociclib + letrozole *versus* letrozole	Reference
PFS, HR, mean (95% CI)	—	—	0.560 (0.460–0.680)	Finn *et al.*[27]
OS, HR, mean (95% CI)	—	—	0.840 (0.492–1.345)	Finn *et al.*[27]
ORR, OR, mean (95% CI)	1.42 (1.20–1.66)	—	1.23 (1.03–1.44)	Calculated
PFS *versus* palbociclib + letrozole	1.010 (0.730–1.390)	—	—	Eisenhauer *et al.*[28]

CI, confidence interval; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

aBC treatment, which involves 21 days on followed by 7 days off therapy. Half-cycle (mid-cycle) corrections were applied to both costs and effectiveness. A discount rate of 5% was applied to both cost and effectiveness estimates.[29]

Clinical efficacy

Lifetime PFS and OS were estimated based on parametric survival analysis of individual patient data from the MONALEESA-2 study (data cut-off, 2 January 2017) according to the investigator-assessed estimates for ribociclib plus letrozole and letrozole arms. The type of model for each endpoint was selected following the recommendations set by the decision support unit at the UK National Institute for Health and Care Excellence (NICE), and published by Latimer *et al.*[30] First, the hazard proportionality was assessed by log-cumulative hazard functions. If the curves were parallel, the proportional hazards assumption was satisfied and the endpoint survival was analyzed using a proportional hazards model. If not, the proportional hazards assumption does not hold and independent survival models were fitted to data from each study arm. The best fitting models were selected based on internal goodness of fit assessed using the Akaike information criterion (AIC), visual inspection of the fit of the model to Kaplan–Meier curves, and on assessment of the clinical plausibility of long-term survival projections. Survival analysis was conducted using the FlexSurv package[31] in R.

For the palbociclib plus letrozole comparison, the efficacy of treatment for both PFS and OS was based on the estimate of hazard ratio (HR) derived from matching-adjusted indirect comparison (MAIC) *versus* letrozole[32] and applied to the letrozole arm of the model. Indirect comparisons were done using data from MONALEESA-2 and a pair-wise meta-analysis of PFS results from both PALOMA-1 and PALOMA-2 trials (Table 1).

PFS

For PFS, the assessment of log-cumulative hazard functions indicated that a proportional hazards model would not be appropriate (Supplemental Material 1). A series of independent models were subsequently fitted to data from each arm of MONALEESA-2 to project long-term PFS. After evaluation of the AIC goodness of fit statistics and visual inspection of the fit of the model to the Kaplan–Meier curves (Supplemental Material 2–4), the extrapolation of PFS was validated through consultation with a clinician. The gamma distribution was the preferred option for the proposed base-case analysis in both arms because clinical validation and statistical goodness of fit were considered equally important. The Weibull model was also a plausible alternative.

OS

For OS, assessment of log-cumulative hazard functions indicated that a proportional hazards model would not be appropriate (Supplemental Material 5). A series of independent models were subsequently fitted to data from each arm of MONALEESA-2 to project long-term OS. Given the lack of differentiation in internal goodness of fit for the conventional distributions and the immaturity of OS in MONALEESA-2, the preferred option for base-case analysis was chosen based on the clinical plausibility of long-term OS projections. Because the extent to which the addition of a CDK4/6 inhibitor to letrozole would increase OS is currently unknown in this population profile, a conservative definition of 3–4%

absolute improvement in the probability of OS over the follow-up was estimated by the expert. Four models (Weibull, gamma, Gompertz, and log logistic) generated landmark survival probabilities that fell within the clinical expert prediction at 5 or 20 years for either the ribociclib arm or the letrozole arm

All other distributions predicted survival rates that were out of the expert's range of plausible values. The gamma distribution was the option chosen for the proposed base-case analysis for both arms, with the Weibull model also being a plausible alternative (Supplemental Material 6–8).

Response rate

The response rate was modelled based on the objective response rate. For both ribociclib and palbociclib, the proportion of responders was estimated by combining the probability of response in the letrozole and placebo group of the MONALEESA-2 trial with the odds ratios of the event comparing treatment *versus* letrozole (Supplemental Material 9). The odds ratios of events were sourced from an unpublished network meta-analysis and were defined as 1.42 (95% CI: 1.20–1.66) for ribociclib plus letrozole and 1.23 (95% CI: 1.03–1.44) for palbociclib plus letrozole (Table 1).

Costs

All costs are expressed in both US dollars and Brazilian reals in the main text, using an exchange rate of 1: 5.5. The direct healthcare costs considered in the model included drug acquisition, health state routine disease monitoring (including CDK 4/6-inhibitor-specific monitoring exams), subsequent treatment lines, management cost for adverse events, and end-of-life care.

Drug acquisition costs

Letrozole cost was estimated using the monthly drug cost multiplied by the time spent in the PF state assuming that therapy is discontinued if there is evidence of PD. The duration of treatment for add-on therapy with either ribociclib or palbociclib was modelled independently of PF using survival data on the time from randomization to treatment discontinuation. This approach was preferable because of treatment-limiting adverse events with CDK 4/6 inhibitors leading to discontinuation of add-on therapy prior to progression, reflecting the shorter duration of add-on therapy compared to PFS. Because there are no patient-level data or published Kaplan–Meier plots available for palbociclib for time to discontinuation, it was necessary to model palbociclib treatment duration using the ribociclib curve adjusted by PFS HR to account for any differences in duration between add-on therapies. Therefore, the HR applied in the model was obtained from MAIC meta-analysis of PFS, on the assumption that differences in treatment duration were proportional to any differences in PFS comparing ribociclib with palbociclib.[32] The resulting HR was 1.01 for palbociclib *versus* ribociclib (95% CI 0.730–1.390; Table 2).

As with PFS and OS, the time to treatment discontinuation (TTD) in the ribociclib group was modelled through parametric survival modelling of patient-level data from MONALEESA-2. AIC showed minimal difference in values between these models, suggesting that all provide reasonable predictions of the trial data (Supplemental Material 10 and 11). The TTD Weibull extrapolation, although having the lowest AIC statistics, crosses the PFS curve in the long term. Thus, the exponential distribution was chosen for the base case.

The cost of drug acquisition was calculated using the list price of medication and the mean total dose of therapy administered in each cycle of the simulation. In the base case, the list price of medication is obtained from the 2019 list issued by Câmara de Regulação do Mercado de Medicamentos (CMED) 2019.[33] Some variability is expected in these prices, reflecting the tax rates practiced by each Brazilian state, without however, a major impact on the final price. For ribociclib, the total drug acquisition costs were estimated based on the proportion of patients receiving each dose of therapy in MONALEESA-2 trial (Table 2). Data from MONALEESA-2 were used to model the proportion of patients on each dose from months 1 to 16. The proportions observed at the end-of-study follow-up (i.e. month 16) were applied to all months thereafter. This rationale was not applied for palbociclib because in Brazil palbociclib has a flat price scheme (i.e. all strengths having the same list price). For palbociclib, drug wastage for dose reduction was also considered, assuming 22% of patients switching from 150 mg to 100 mg and 14% switching from 100 mg to 75 mg. For ribociclib, no drug wastage was assumed as it is only

Table 2. CMED 2019 list price for therapies used in the model.

Therapy	Daily dose (mg)	Monthly dose (mg)	Pack size	Strength (mg)	Pack price (USD)	Monthly cost (USD)	Total cost (USD)/month∫
Ribociclib	600.0	10,889.0	63	200.0	2757	2383	2383
	400.0	7259.3	42	200.0	1838	1588	1588
	200.0	3629.7	21	200.0	919	794	794
Palbociclib	125.0	2653.8	21	125.0	2842	2873	2873
Letrozole (monotherapy and association with ribociclib and palbociclib)	2.5	76.1	28	2.5	115	125	125
Fulvestrant (initial)	500.0	1087.1	2	250.0	1251	2721	2769
(Follow-up dose)	500.0	543.5	2	250.0	1251	2721	2769
Chemotherapy*							1143
Tamoxifen	20.0	608.8	30	10.0	19	39	39
Anastrozole	1.0	30.4	28	1.0	130	141	141
Exemestane	25	760.9	30	25 mg	USD 138	140	140
Everolimus	10	304	30	10 g	USD 2270	2303	2303

*The price of chemotherapy represents an average price of some schemes and molecules (Supplemental material 13).
∫include the administration costs.
CMED, Câmara de Regulação do Mercado de Medicamentos; USD, US dollar.

available in 200 mg tablets across all strengths, thus facilitating dose adjustment without the need for a new prescription.

Since administration of oral drugs is not reimbursed by payers in Brazil, no cost for drug administration was considered. For intravenous therapy, the assumed costs for drug administration were based on the 5th edition of Classificação Brasileira Hierarquizada de Procedimentos Médicos (CBHPM;[34] Table 3).

Health state routine disease monitoring costs

The costs of disease monitoring are dependent on the PF and PD status of the population, with PD being associated with a higher cost burden relative to PF disease. These costs were estimated using a macro costing approach based on national clinical guidelines for BC[35] and advice from a clinical expert panel (Table 3). There are great uncertainties associated with these costs, but as the sum is irrelevant compared to the cost of treatments, there is no impact on the final result.

The monthly cost of drug monitoring was also considered for patients receiving ribociclib and palbociclib to take into account additional monitoring specific to these therapies. In this sense, the costs of monitoring with add-on therapy included liver function tests and electrocardiograms performed for the duration of treatment (Table 3). For letrozole, the costs of drug monitoring were captured through routine disease monitoring costs assigned to the PF and PD health states.

The drug monitoring costs were calculated from the unit cost of monitoring resources multiplied by the number of resources consumed during the following months. Monitoring costs comprise biochemistry tests, complete blood counts, and electrocardiograms to support the monitoring of endocrine therapy (Table 3).

Subsequent treatment line costs

The costs of subsequent treatment lines were considered for patients receiving second-line therapy after progression on first-line therapy and for

Table 3. Health resources and costs.

PFS				
Resource item	**%. of patients**	**Resource used**	**Unit cost (USD)**	**Cost (USD)/month**
Healthcare professional visits				
General practitioner visits	100	1.0	17	17.0
Oncology consultant office	33	1.0	17	5.6
Hospitalization				
Hospitalization (general)	1	8.0	127.5	10.2
Hospitalization (oncology)	1	6.0	127.5	7.7
Monitoring				
Biochemistry test	33	1.0	6.4	2.1
Blood test	30	1.0	2.9	0.9
Imaging				
Bone scintigraphy	8	1.0	66.5	5.3
Bone X-ray	3	1.0	11.1	0.3
Chest X-ray	3	1.0	11.1	0.3
Computer tomography scan	20	1.0	206.5	41.3
Total				90.7
Progressed disease				
Healthcare professional visits				
General practitioner visits	100	1.0	17	17
Oncology consultant office	100	0.5	17	8.5
Outpatient (ambulatory care)	100	0.2	43	8.6
Hospitalization				
Hospitalization (oncology)	100	0.5	127.5	63.8
Monitoring				
Biochemistry test	33	1.0	6.4	2.1
Blood test	30	1.0	2.9	0.9
Electrocardiogram	4	0.1	8.2	0.03
Imaging				
Computed tomography scan	52	0.5	206.5	53.7
Liver ultrasound	13	0.1	27.8	0.4
Magnetic resonance imaging	15	0.3	207.3	9.3
Positron emission tomography	13	0.3	494.2	19.3
Total				183.6
Cost of administration for infusion treatments	100	1	88.4	88.4

(Continued)

Table 3. (Continued)

Add-on treatment monitoring	Unit cost (USD)	Value	Ribociclib + LZE	Palbociclib + LZE
			% of patients	% of patients
Liver function test	5.1	4.0	100	0
Complete blood count	2.8	4.0	100	100
ECG	8.2	3.0	100	0
Total			USD 56.4	USD 11.3
Monthly treatment monitoring	**Unit cost (USD)**	**Value**	**Ribociclib + LZE**	**Palbociclib + LZE**
			% of patients	% of patients
Liver function test	5.1	1.0	100	0
Complete blood count	2.8	1.0	100	100
ECG	8.2	0.0	0	0
Total			USD 7,9	USD 2.8
End-of-life costs			**% of patients**	**Unit cost (USD)**
Composite costs			100%	2806.4
Adverse events				**Unit cost (USD)**
Diarrhea				540.9
Fatigue				79.8
Infection				968.0
Nausea				416.4
Febrile neutropenia				3506.2
Pulmonary embolism				471.5
Vomiting				416.4

PFS, progression-free survival; Prop, proportion; pts, patients; LZE, letrozole; ECG, electrocardiogram; USD, US dollar.

patients receiving third-line therapy after progression on second-line therapy. For patients in the second-line setting, it was assumed that 60% were on ET treatment and 40% on chemotherapy. For third-line settings, patients were further categorized as 70% receiving either ET or chemotherapy and 30% as not receiving any active treatment. The total cost of subsequent treatment was calculated by multiplying the distribution of treatments, the expected total duration of each treatment in months, and the monthly cost of each treatment. The duration of each subsequent treatment line was obtained from the literature and the distribution of the chemotherapy, targeted therapies, and ETs administered as subsequent treatments were determined by the expert clinical panel (Supplemental Material 12). The costs were retrieved from the CMED 2019 list pricing for each treatment option (Table 2). For chemotherapy, the average price is represented by a mean value of several options of treatment and their respective posology used as either monotherapy or combined therapy (Supplemental Material 13).

Management cost for adverse events

The frequency of grade 3 or above adverse events for each treatment strategy was obtained from clinical studies (Supplemental Material 14). Adverse event management costs were applied as

a one-off cost at the start of the model evaluation on the assumption that severe events occur during the first 12 months of treatment, as documented in clinical trials of CDK 4/6 (Table 3). These events include diarrhea, fatigue, infection, nausea, febrile neutropenia, pulmonary embolism, and vomiting. Severe infections, febrile neutropenia, and nausea were more commonly reported in ribociclib patients than placebo patients in MONALEESA-2 and were also considered. Pulmonary embolism was included as an adverse event as increased incidence was observed in the palbociclib arm in the PALOMA-1 study.[27]

End-of-life costs

A fixed amount was attributed for the end-of-life costs. It was composed of estimates of hospitalization and services performed at home, based on expert opinion (Table 3).

Health benefits

The valuation of health benefits in the model was based on the QALY gained.

Utility

To estimate the number of QALYs for each therapy, health state utility (HSU) values are required to appropriately weight the time spent alive in each health state. The quality of life variable was modelled using HSU values derived from EQ-5D data collected in MONALEESA-2 and from data identified through a literature review of HSU studies. In MONALEESA-2, EQ-5D-5L data were collected during the screening phase, every 8 weeks during the first 18 months and then every 12 weeks thereafter, until disease progression, and at the end of treatment. A summary of the domain scores for the EQ-5D-5L collected in MONALEESA-2 is presented in the Supplemental Material 15.

HSU data from MONALEESA-2 were modelled using a repeated-measures mixed-effects model fitted to all observations of HSU taking into account the repeated structure of observations, under the assumption that data are randomly missing. This provided HSU values for PF state (objective response and stable disease) considering all measures of EQ-5D recorded in the study (Table 4). For PD state, the limited number of observations did not provide reliable estimates, and thus the values reported by Lloyd *et al.*[36] were considered (Table 4).

Table 4. Utilities value used in the model.

Health state utility values, mean (SE)		References
PFS		
CR/PR	0.834 (0.0068)	Calculated
Stable disease	0.829 (0.0063)	Calculated
PD	0.505 (0.0505)	Jackson[31]
AE disutility values		
Diarrhea	−0.006	Tremblay *et al.*[32]
Fatigue	−0.029	Tremblay *et al.*[32]
Infection	−0.05	Tremblay *et al.*[32]
Nausea	−0.021	Tremblay *et al.*[32]
Febrile neutropenia	−0.012	Tremblay *et al.*[32]
Pulmonary embolism	−0.05	Tremblay *et al.*[32]
Vomiting	−0.05	Tremblay *et al.*[32]

AE, Adverse events; CR, complete response; PD, progressed disease; PFS, progression-free survival; PR, partial response; SE, standard error.

The impact of adverse events on the HSU values of the population was obtained from the study by Hudgens *et al.*[37] Disutility values (1-HSU) by adverse events as well as the assumed utilities values are summarized in Table 4.

Sensitivity analyses

The uncertainty associated with the model's parameters and the robustness of results were evaluated using deterministic (univariate analysis) and probabilistic sensitivity analyses (PSAs).

Deterministic sensitivity analysis

A one-way deterministic sensitivity analysis was undertaken by varying each key parameter (Supplemental Material 16). For discount rate, the lowest value adopted was 3.5%, which represents the value assumed by many countries.[38] The highest value was empirical, assumed as 6%. The cost parameters were varied by ±25% and the cost of ribociclib was only assumed to vary by 10% less than the list price. All the other parameters were considered to vary by ±10%. The

Table 5. Main results of the model.

	Comparison between ribociclib and palbociclib		Comparison between ribociclib and letrozole	
	Ribociclib + LZE	**Palbociclib + LZE**	**Ribociclib + LZE**	**Letrozole**
Total cost	USD 72,091.8	USD 92,749.6	USD 83,058.7	USD 29,215.1
Total QALYs	3.30	3.16	3.84	2.61
Incremental cost	–USD 20,657.8		USD 53,843.6	
Incremental QALY	0.14		1.23	
ICER	Ribociclib is dominant		USD 43,826.9/QALY	

ICER, incremental cost-effectiveness ratio; LZE, letrozole; QALY, quality-adjusted life year; USD, US dollar.

lowest value for the time horizon was defined as 20 years. Utility values varied by ±0.1. For palbociclib HR PFS and OS estimates, the lower and higher 95% confidence interval values from the indirect comparison were used.

Probabilistic sensitivity analysis

The key parameters in the PSA included clinical, cost, and utility data. A total of 1000 simulations were performed using the Monte-Carlo method.[39] To conduct a PSA, probabilistic distributions selected following the recommendations outlined in handbooks of health economic evaluation were assigned to each input in the model and used to randomly select new plausible values.[40]

Results

The total cost of treatment with ribociclib plus letrozole was USD 72,091.82 (BRL 396,505) *versus* USD 92,749.64 (BRL 510,123) for palbociclib plus letrozole. Total QALYs for each treatment were 3.30 for ribociclib plus letrozole and 3.16 for palbociclib plus letrozole (Table 5). For the comparison with letrozole monotherapy, the total cost of treatment with ribociclib plus letrozole was USD 83,058.73 (BRL 456,823) *versus* USD 29,215.10 (BRL 160,683) for letrozole monotherapy. Total QALYs were 3.84 for ribociclib plus letrozole *versus* 2.61 for letrozole monotherapy (Table 5).

The results of the base-case analysis showed that ribociclib is dominant over palbociclib for the first-line treatment of women with HR+/HER2− aBC, which means that ribociclib plus letrozole treatment was associated with a cost reduction of USD 20,657.82 (BRL 113,618) and a gain of 0.14 QALYs compared with palbociclib plus letrozole (Table 5).

Compared with letrozole monotherapy, ribociclib plus letrozole was associated with an incremental cost of USD 53,843.64 (BRL 296,140) and an incremental QALY gain of 1.23, corresponding to an incremental cost-effectiveness ratio (ICER) of USD 43,826.91 (BRL 241,048) per QALY gained (Table 5).

Sensitivity analysis

According to the deterministic sensitivity analysis, for the comparison of ribociclib plus letrozole with palbociclib plus letrozole, the lower discount rate in benefit was the most impactful parameter, followed by ribociclib price (Supplemental Material 17). For the comparison with letrozole, both discount rates in benefit and cost were the most impactful parameters, followed by ribociclib price (Supplemental Material 18).

According to the PSA, ribociclib plus letrozole remained dominant *versus* palbociclib plus letrozole with a mean incremental cost reduction of USD 21,191.82 (BRL 116,555) and a mean increase of 0.097 QALYs. Regarding the robustness of the model, despite some uncertainty, most of simulation points are concentrated in the dominance quadrant (Supplemental Material 19).

When compared with letrozole, ribociclib plus letrozole was associated with an incremental cost of USD 55,051.10 (BRL 302,781) and incremental QALY gain of 1.245, with ICER of USD 44,208.55 (BRL 243,147) per QALY gained (Supplemental Material 20).

Discussion

According to the present model, ribociclib in combination with letrozole was dominant over palbociclib plus letrozole, in other words, less expensive and slightly superior in effectiveness. When compared with letrozole, our results suggest that combined treatment with ribociclib and letrozole provides significant gains in effectiveness, with additional costs for the healthcare system.

The results obtained by comparison with palbociclib are not surprising when considering the dosing regimen and pricing scheme of both CDK 4/6 inhibitor alternatives. Ribociclib has the advantage of not requiring a new prescription, and therefore avoiding wastage, in the context of dose reductions for adverse event management (given the single 200 mg strength). More importantly, ribociclib has a linear pricing structure (per mg), which generates savings in case of dose reductions. Conversely, palbociclib is available in three different strengths (tablets of 125 mg, 100 mg and 75 mg), resulting in drug wastage when dose reduction is needed. In addition, it has a flat pricing structure for all three dosages in most countries, including Brazil, which impacts the cost of treatment when compared with ribociclib, because dose reductions are necessary in a significant proportion of patients.[9,16,17,41] Regarding effectiveness, there is still uncertainty regarding OS differences between both CDK 4/6 inhibitors, and both studies, MONALEESA-2[9] and PALOMA-2,[22] are still ongoing due the immaturity of OS data. For the PFS outcome, the magnitude of the effect is almost the same, with no statistically significant differences between therapies.[42] Nonetheless, it is important to note that, when compared with fulvestrant monotherapy, ribociclib plus fulvestrant has demonstrated superior OS for both first and second-line treatment of aBC,[20] which was not the case for palbociclib.[25] Ribociclib, in combination with AIs, has also demonstrated clinical and statistical OS superiority in peri/premenopausal women.[19]

Our findings are supported by other cost-effectiveness studies. Mistry *et al.*,[43] using the same model design, have also shown that ribociclib is dominant over palbociclib from a US payer perspective. Galve-Calvo *et al.*[44] found an ICER of USD 1830.95 (€1543.62) per QALY gained, showing that ribociclib plus letrozole would become the first-line treatment of choice for postmenopausal women with HR+/HER2− aBC following a reduction of as little as 0.50% in the price of ribociclib, providing greater effectiveness together with economic savings. These authors also argue that the degree of dominance of ribociclib over palbociclib, both in combination with letrozole, would be more marked in the scenario of price parity, in which the economic benefits of using a CDK4/6 inhibitor plus letrozole would result in savings of USD 19,359.42 (€16,321.32) per patient treated with ribociclib plus letrozole compared to palbociclib plus letrozole.

When compared with letrozole, the model estimated an ICER of USD 43,826.91 (BRL 241,048) per QALY. Judging whether this result is cost-effective or not is a challenge in Brazil, since there is no formally defined cost-effectiveness threshold. However, using a threshold equivalent to three times the gross domestic product (GDP) *per capita* as originally recommended by the World Health Organization[45] is a valid means for prioritization of health technologies. This threshold is justified by the assumption that a country should be willing to pay as much for 1 year of life as an average person would produce that year. However, the World Health Organization later withdrew the recommendation, arguing that this threshold does not have the necessary specificity for decision-making in all countries, possibly leading to erroneous decisions in the allocation of resources.[46] In any case, even in situations where a threshold is formally defined, cost-effectiveness should not be the only criterion for decision-making in countries that adopt Health Technology Assessment as part of the process of incorporating new technologies,[47] as is the case of Brazil. Many other domains affect decision-making with similar weights, such as the organization of the health system, the costs of implementing change, political issues, the perspective and valuation of the benefit of a given technology by the society, importance of the clinical condition, and budget impact analysis.[48]

Even if all interventions had ICERs below the accepted willingness-to-pay threshold, in many countries, health budgets would still be insufficient to ensure access to all these interventions.[49] Therefore, budget impact analysis is another important aspect to be considered, especially because it addresses affordability, which is not entirely contemplated in cost-effectiveness analyses.[50] Another relevant aspect for consideration within a context such as that outlined in the present study is the level of clinical priority of the proposed technology. The relevance of BC is

unquestionable, especially in advanced settings. Metastatic BC is an incurable disease, and therefore the treatment goals should be to optimize survival and quality of life while maintaining and acceptable safety profile, all of which are met with ribociclib. Ribociclib has already been incorporated in many healthcare systems, in countries like Canada,[51] England,[52] Sweden,[53] and Australia,[54] but not yet in Brazil. Thus, the lack of access to this treatment may be perceived as an important gap, considering the important benefits for patients, such as improved PFS and OS. The hurdle stems from budget constrains; the share of GDP allocated to health spending is only 4.4% for the private healthcare sector in Brazil (55% of the total of the total private health expenditure),[55] supposedly to cover all therapeutic areas, including cancer. In this context, the reimbursement of ribociclib remains a challenge, despite the unquestionable and unprecedented clinical benefit, requiring assessment vis-à-vis other technologies within a Health Technology Assessment framework.

From a clinical point of view, CDK 4/6 inhibitors have become the standard of care for HR+/HER2− aBC, recommended by the main national[6,56,57] and international[58–60] clinical guidelines. This fast change in clinical practice may be justified by the degree of clinical benefit achieved with this treatment, reflected by a clinically and statistically significant gain in OS. It should be noted that OS is the hardest outcome to achieve in a clinical trial, and the most desirable in any oncology study. The OS outcome, defined as the time from patient randomization to death, is an objective measure with direct interpretation; as a measure, it reflects the effectiveness and safety of the intervention. However, it is influenced by the effectiveness of subsequent post-progression therapies (and consequently by the median post-progression survival time) or crossover treatments,[61,62] complicating the demonstration of statistically significant differences between treatment arms in a trial. Although data are still immature in the MONALEESA-2 trial, so far ribociclib is the only CDKi 4/6 associated with OS gains in first-line[19,20] and second-line[20] treatment, which have been observed regardless of combination partner (AI[19] or fulvestrant[20]) or menopause status (pre,[19] peri[19] and postmenopause[20]). The magnitude of the benefit has been consistent across trials, with a risk reduction in death estimated at 30%, drastically decreasing uncertainties regarding benefit.

Our study has strengths and limitations. A robust model was developed using a cohort-based partitioned survival approach, the type of model used in 73% of the proposals submitted to the NICE in the oncology field, especially in the metastatic setting.[63] The assumptions adopted were conservative, for example, assuming the same utility values for the treatments or assuming a much lower ribociclib advantage in OS than evidenced by current trials. Our sensitivity analyses underscored the robustness of the model, confirming the conclusions reached for the base case. Limitations include both structural and parametric uncertainties that are inherent to all cost-effectiveness models and should always be considered, regardless of the trend of the results.[64,65] In Brazil, only scarce evidence is available around healthcare resource consumption, such as patient monitoring, management of adverse events, and treatment of progression. Because of that, some of these parameters had to be validated by expert opinion, and others were obtained from payer claim databases.

Finally, for chronological reasons, it was not possible to compare the ICER of ribociclib *versus* abemaciclib, the third representative of the class, in order to have a more complete landscape of the three CDK4-6 inhibitors available in clinical practice. At the time the model was developed, in 2018, abemaciclib was not a therapeutic option in Brazil, which is why it was not considered a comparator of the model. Palbociclib was the first representative of the class to be registered with the Brazilian Regulatory Agency on 5 February 2018.[66] On 30 July of the same year,[67] ribociclib was additionally registered. Abemaciclib was not registered until the following year, on 11 March 2019.[68] In a recent unpublished literature review conducted by our group, no comparative cost-effectiveness studies with abemaciclib were found, neither with palbociclib nor with ribociclib. A single study comparing healthcare costs in patients treated with CDK4/6 inhibitors in real-world clinical practice was identified using a large US commercial claims database. This study, conducted from a payers' perspective, included medical and pharmacy costs as well as inpatient and outpatient costs from 4320 patients in first-line to third-line or later treatment. The results showed that total healthcare costs appeared to be highest with abemaciclib than with the other CDK 4/6 inhibitors.[69] Another important aspect to be commented on is the economic advantage that ribociclib maintains over abemaciclib. In Brazil, although both ribociclib and abemaciclib present

a linear price reduction to dose reduction, abemaciclib is marketed in different presentations, which often leads to drug wastage when there is a need to reduce the dose to manage adverse events. In this respect, ribociclib is likely to be superior to abemaciclib, but further studies to confirm these findings are warranted.

Conclusions

Overall, the evidence supports ribociclib as a potent, selective, and well-tolerated orally active CDK 4/6 inhibitor that offers substantial clinical benefit for patients with HR+/HER2− aBC. As demonstrated by the cost-effectiveness dominance over palbociclib, ribociclib produces cost savings for the healthcare system and QALY gains when used as first-line treatment in postmenopausal women with HR+/HER2− aBC. Considering the most relevant outcomes for these patients, represented by clinically and statistically significant differences in PFS and OS, ribociclib should be considered for incorporation in the Brazilian private healthcare system.

Conflict of interest statement

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Supplemental material

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