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Cost-effectiveness of ribociclib as initial treatment for premenopausal women with advanced breast cancer in Singapore

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Abstract

Background: CDK4/6 inhibitors have shown promising results for treating advanced breast cancer (ABC) and are routinely used in Singapore. In view of their high costs, it is important to assess their relative value compared to existing standards of care in the local setting.

Aims: This study evaluates the cost-effectiveness of adding ribociclib to goserelin and a nonsteroidal aromatase inhibitor or tamoxifen as initial therapy for premenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) ABC in Singapore.

Methods: A partitioned survival model with four health states (progression-free on first-line treatment, progression-free on second-line treatment, progressed disease, and death) was developed from a healthcare system perspective over a 10-year time horizon. Key clinical inputs were derived from the MONALEESA-7 trial, and survival curves were extrapolated beyond the trial period. Health state utilities were derived from the literature and direct medical costs were obtained from local public healthcare institutions. A discount rate of 3% was applied to both costs and outcomes. One-way deterministic and probabilistic sensitivity analyses were conducted to explore uncertainties.

Results: The base-case analysis resulted in an incremental cost-effectiveness ratio (ICER) of SGD197, 667 per quality-adjusted life-year. Sensitivity analyses showed that the ICER was sensitive to the survival parametric distribution, ribociclib price, time horizon, and utility weights used. Even when these were varied, ICERs remained high and not cost-effective in the local context.

Conclusion: At its current price, adding ribociclib to endocrine therapy is unlikely to be cost-effective in Singapore for HR+, HER2− ABC. Results from this study are useful to inform future funding decisions for CDK4/6 inhibitors alongside other factors including clinical effectiveness, safety, and budget impact considerations.

1 | BACKGROUND

Breast cancer is the most prevalent cancer among women in Singapore, accounting for 29% (*n* = 10 824) of all female cancers from 2013 to 2017.[1] It was also the leading cause of cancer-related deaths among women in Singapore (17% of all cancer deaths in women) for the same period.[1] While breast cancer is predominantly diagnosed in postmenopausal women, breast cancer rates in premenopausal women have been increasing. In Asia, more than 40% of breast cancers are diagnosed in women <50 years, compared with 20% in Western countries.[2] Hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) is the most common breast cancer subtype[3] and younger women with HR+ tumors tend to have a poorer prognosis than older women.[4]

Cyclin-dependent kinase (CDK)4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) have shown promising results and have transformed the treatment landscape for HR+, HER2− advanced breast cancer (ABC). They are increasingly being used as standard of care with endocrine therapy (ET) in both first- and later-line settings. While there are no head-to-head trials comparing CDK4/6 inhibitors with each other, they have demonstrated remarkably similar efficacy but different toxicity profiles. Palbociclib and ribociclib are associated with more myelosuppression whereas diarrhea is more common with abemaciclib. Ribociclib has been associated with QT prolongation, and hepatic dysfunction was reported with both ribociclib and abemaciclib.[5-7] As the current market leader in Singapore, palbociclib is most commonly used locally and is preferred due to fewer monitoring requirements compared to other agents. To date, none of the phase 3, first-line studies of CDK4/6 inhibitors have reported overall survival (OS) results or have been studied in premenopausal women except for ribociclib, which demonstrated a significant OS benefit in MONALEESA-7.[8] Published cost-effectiveness analyses (CEAs) of palbociclib and ribociclib so far have focused on postmenopausal women and have consistently reported high incremental cost-effectiveness ratios (ICERs) based on immature OS data or data from a phase 2 study which showed no OS benefit.[9-13] With the OS results seen with MONALEESA-7, we hypothesized that this could improve cost-effectiveness of this treatment strategy. This study evaluates the cost-effectiveness of first-line ribociclib with ET in premenopausal women, an underrepresented but increasingly important subgroup of patients in Singapore.

2 | METHODS

Clinical inputs for the model were mainly derived from the MONALEESA-7 study. At a median follow-up of 34.6 months, ribociclib was associated with significantly improved progression-free survival (PFS; hazard ratio [HR] = 0.55, 95% CI 0.44 to 0.69; *p* < .0001) and OS (HR = 0.71, 95% CI 0.54 to 0.95; *p* = .00973).[8,14]

2.1 | Model structure

An Excel-based partitioned survival (areas under the curve) model was developed from the Singapore healthcare system perspective (comprising government subsidies, insurance, and patient co-payments) to assess the cost-effectiveness of adding ribociclib to first-line ET (goserelin plus either letrozole, anastrozole, or tamoxifen) compared to ET alone (placebo) in premenopausal women with HR+, HER2− ABC. The model included four health states: first-line progression-free (PF1), second-line progression-free (PF2), progressed disease on second- or subsequent-line treatment (PD), and death (Figure S1). All patients were assumed to enter the model in the PF1 state. The proportion of patients in each health state at each time point was calculated from the Kaplan-Meier (KM) OS and PFS curves from the MONALEESA-7 trial. At the beginning of each cycle, patients remained in the PF1 state until they progressed and transitioned to PF2 or died. Second-line PF (PF2) represented the time to disease progression between first- and second-line treatment cessation. In the PF2 state, patients received a second-line treatment and stayed in this state until their disease progressed, and they transitioned to the PD state, or until they died. The PD state represented the time from second-line therapy cessation until death, and in this state, patients received subsequent lines of treatment, and/or supportive or palliative care. A time horizon of 10 years with a cycle length of 28 days was used in the base case, which was deemed to be sufficiently long enough to capture most of the survival benefits and costs accrued, considering that the 10-year survival rate for women (<50 years) with ABC is approximately 15%.[15] A discount rate of 3% was applied to both health outcomes and costs.

2.1.1 | Treatment pathway

Patients were assumed to receive either ribociclib 600 mg (3 × 200 mg tablets) orally once daily for 21 days followed by a 7-day break every 28 days or placebo in addition to goserelin and either letrozole, anastrozole, or tamoxifen until disease progression. Choice of ET, and distributions of second-, third-, and subsequent line therapies or "treatment mix" were extrapolated from MONALESSA-7 in the base case (Table S1). Of note, in the trial, only 69% and 75% of patients in the ribociclib and placebo arms, respectively, received second-line treatment which is lower than local practice where 95% of patients would proceed to second-line treatment. In both the trial and local practice, we assumed approximately 85% of patients would proceed to third or subsequent line treatment. According to local experts, the treatment pathway for ABC is complex and choice of second- and subsequent line therapies is highly variable and thus "treatment mix" was varied in a scenario analysis to capture the likely treatments used locally in patients who received ET with or without a CDK4/6 inhibitor as initial therapy (Table S1).

2.2 | Model parameters

2.2.1 | Clinical efficacy data

Areas under the PFS and OS curves in MONALEESA-7 were used to determine the mean time that patients remained in each health state. As patient level data were not available, individual data points from the

published KM curves for PFS and OS were extracted using the WebPlotDigitizer[16] and the Guyot curve fitting approach was used to estimate the underlying survival distribution from the digitized KM graphs.[17] Actual data from the KM curves were used until the end of the 3-year follow-up period, after which parametric functions were fitted onto the remaining data to extrapolate the long-term survival until the end of the time horizon. Candidate functions for the parametric extrapolation were the exponential, Weibull, log-normal, log-logistic, Gompertz, and generalized gamma distributions. Goodness-of-fit of these functions were assessed using the Akaike Information Criterion (AIC) and a visual inspection of the parametric curves against actual data. For OS, the AIC scores for the log-logistic and Gompertz distributions were the lowest among the six candidate functions for ribociclib and placebo, respectively (Table S2). However, extrapolated data from these distributions led to clinically unlikely survival endpoints (53% for ribociclib, [Figure S2] 19% for placebo [Figure S3], respectively, after 5 years) relative to reported local 5-year OS rates for women with metastatic breast cancer (27%)[1] and survival rates from outside Singapore (up to 40%).[18] Furthermore, overseas registries have also reported 10-year breast cancer-specific survival rates ranging from 15% to 16%[15] which also deviated from these distributions at this time point (28% for ribociclib [Figure S2] 0% for placebo [Figure S3]). In both treatment arms, the Weibull distribution had the next lowest AIC scores and fitted well with the actual curves with more realistic 5- and 10-year OS rates of 39% and 8% for placebo and 49% and 15% for ribociclib, respectively. Considering both visual fit and clinical plausibility, the Weibull distribution was chosen for the base-case analysis to extrapolate OS for both treatment arms.

For PFS, visual inspection and AIC values (Tables S3 and S4) showed that the distributions fitted well with the actual KM curves. However, only the Weibull and exponential distributions for PF1 and Weibull and generalized gamma for PF2 were clinically plausible for both treatment arms as all other distributions had elongated tail ends (Figures S4–S7). The Weibull distribution for both PF1 and PF2 were chosen for the base case.

As patients were not allowed to continue study treatment on disease progression in the trial, and disease progression was the most common reason for treatment discontinuation (75%-80%), PFS curves were also used to estimate time on treatment. The difference between PF2 and PF1 PFS curves was used to estimate treatment and disease management costs for patients receiving second-line treatment in the model. As time spent on third and subsequent line therapies was not available and assuming that most patients remained on active treatment until they die, time spent on third and subsequent line therapies was subsumed within the PD state and was estimated as the difference between OS and PF2. In the absence of long-term data, the treatment effect of ribociclib was assumed to last for the entire time horizon with scenario analyses limiting treatment effect to 5 and 7 years to account for this uncertainty.

2.2.2 | Utility values

Although utility data were collected in MONALEESA-7 using the European Quality of Life Five Dimensions (EQ-5D) questionnaire, they were not publicly available, and an indirect method was used to estimate the quality-adjusted life-years (QALYs) in the model. A literature search was conducted to identify utility studies in patients with ABC. Two breast cancer utility studies matching our target population were retrieved—a local study using vignettes and the standard gamble (SG) method to measure patient preferences and a Canadian study using the EQ-5D questionnaire to derive health state utility values (HSUVs) (Table S5).[19,20] The Canadian study was selected for use in the base case as participants most closely resembled the disease characteristics and health states of the trial population. Moreover, EQ-5D is the preferred instrument for utility elicitation by several health technology assessment (HTA) agencies.[21,22] A scenario analysis was conducted using the local HSUVs to assess their impact on the ICER.

In MONALEESA-7, patients in the ribociclib arm experienced more grade ≥ 3 neutropenia, hepatotoxicity, and prolonged QT interval than those in the placebo arm (Table 1). As local experts advised that these adverse events (AEs) were manageable and unlikely to affect quality of life, utility decrements for AEs were not included in the model.

2.2.3 | Resource use and cost data

Only direct medical costs were included in the model, in accordance with the perspective of the analysis. Indirect costs (eg, productivity loss) were not considered. Disease management costs for both treatment arms included cost of drugs, drug administration, pharmacy preparation, medical consultations, CT scans, AE hospitalizations, and end-of-life care. Additional laboratory tests, such as full blood counts, liver function tests, and renal panels, as recommended in the product information,[23-27] were also included for patients receiving a CDK4/6 inhibitor, everolimus, or chemotherapy (Table S6).

Costs of first-, second-, and subsequent line treatments, including drug administration and preparation costs, where relevant, were estimated from prices charged to patients at public healthcare institutions (PHIs) in Singapore. Based on local expert opinion, most AEs, including neutropenia, were easily managed in the outpatient setting. Hence, only AEs requiring hospitalization, febrile neutropenia and grade ≥ 3 hepatic dysfunction, were included in the model. Hospitalization costs were obtained from the Ministry of Health Singapore Casemix and subvention databases (2011-2018). Costs were based on AE rates in MONALEESA-7 and associated hospitalization rates estimated by local experts (Table 1). These costs were applied once to the total life-time costs in the model. Terminal care costs for palliative treatment such as inpatient hospice or home-care hospice visits were also included for the last 28 days of life for each patient who died in the model.

2.2.4 | Outcomes

The outcomes of interest were overall life years (LYs), QALYs, the total costs in both treatment arms, and the ICER.

TABLE 1 Model inputs (base case)

Parameter	Ribociclib +ET	ET alone	Source
Efficacy			
Median overall survival, months (95% CI)	(NR)	40.9 (37.8 to NR)	MONALEESA -7[8]
Median first-line progression-free survival, months (95% CI)	23.8 (19.2 to NR)	13.0 (11.0 to 16.4)	MONALEESA -7[14]
Safety			
Grade ≥ 3 QT prolongation	1.8%	1.2%	MONALEESA -7[8,14]
Grade ≥ 3 neutropenia	63.5%	4.5%	
Febrile neutropenia	2%	1%	
Grade ≥ 3 hepatic dysfunction	9%	2%	
Febrile neutropenia requiring hospitalization	2%	1%	Local expert opinion[a]
Grade ≥ 3 hepatic dysfunction requiring hospitalization	4.5%	1%	
Utility values			Source
PF1	0.73 (0.53 to 0.93)		Lambert[20]
PF2[b]	0.73 (0.53 to 0.93)		
PD[b]	0.64 (0.42 to 0.86)		
Cost of drugs per 28-day cycle (SGD)			Source
Ribociclib	$2929		2018 MOH Drug Utilization data
Palbociclib	$4421		
Abemaciclib[c]	$5600		
Aromatase inhibitor[d,e]	$2		
Tamoxifen[e]	$10		
Exemestane[e]	$31		
Fulvestrant	$1778		
Goserelin	$248		
Everolimus	$4560		
Chemotherapy[f,g]	$87		
Olaparib	$8316		
Alpelisib	$4200		
Cost of treatment administration (SGD)		Frequency	Source
Facility fee/ chair time[h]	$272	Per treatment	PHI, 2019[i]
Chemotherapy preparation fee charged by pharmacy	$53	Per preparation	PHI, 2019[i]

TABLE 1 (Continued)

Parameter	Ribociclib +ET	ET alone	Source
Cost of disease management		Frequency	Source
Consultation visit (senior consultant)	$75	Per visit	PHI, 2019[i]
CT scan	$940	Per scan	
Liver function test	$71	Per test	
Renal panel test	$63	Per test	
Full blood count	$26	Per test	
Lipid panel test	$40	Per test	
ECG	$50	Per test	
Cost of hospitalization for adverse events (SGD)		Frequency	Source
Febrile neutropenia	$3685	Per episode	MOH Casemix & Subvention data 2011 to 2018
Hepatic dysfunction	$2117	Per episode	
Cost of terminal care (SGD)		Frequency	Source
Inpatient hospice	$275	Per day	Hospice centre, 2019[j]
Home care hospice[k]	Free	Per visit	

Abbreviations: CI, confidence interval; CT, computed tomography; ET, endocrine therapy; MOH, Ministry of Health Singapore; NR, not reported; PD, progressed disease on second and subsequent lines of treatment; PD1, progressed disease on first-line treatment; PF1, progression-free on first-line treatment; PF2, progression-free on second-line treatment; PHI, public healthcare institution; SGD, Singapore Dollar.

[a]As hospitalization rates were not available from the trial, we assumed that all patients with febrile neutropenia and 50% of patients with grade ≥ 3 hepatic dysfunction were hospitalized as confirmed by local experts.

[b]The study by Lambert-Orby reported slightly higher utilities in PF2 vs PF1 and PD2 vs PD1 health states. As a conservative approach, PF1 utilities from Lambert-Obry study were used for both PF1 and PF2 model health states. Likewise, PD1 utilities were used for the PD health state in the model.

[c]Based on overseas list price as abemaciclib was not yet marketed in Singapore when the model was constructed.

[d]Based on price to patient for letrozole which is the more commonly used aromatase inhibitor locally.

[e]Available as generics.

[f]Where applicable, cost of drugs assumes patients have an average weight of 60 kg, body surface area of 1.6 m^2 and area under the curve of 6 (for carboplatin dosing).

[g]Based on weighted cost of paclitaxel, doxorubicin, carboplatin, and capecitabine.

[h]Only once per day.

[i]Average selling prices across public healthcare institutions in Singapore

[j]Price charged by one hospice centre in Singapore

[k]Home hospice visit is complimentary by the hospice centre.

2.2.5 | Sensitivity analyses

One-way sensitivity analyses (OWSA) were conducted to explore the impact of uncertain model parameters on the ICER. Each parameter was varied independently by the lower and upper limits of the 95% confidence interval or reported ranges in literature.

TABLE 2 Summary of costs and benefits of adding ribociclib to endocrine therapy, base-case analysis

	Ribociclib + ET	ET alone	Incremental difference
Total cost (SGD)	**$177 589**	**$87 119**	**$90 470**
Drug and management costs	$174 987	$84 420	$90 567
Terminal care costs	$2433	$2641	-$208
AE costs	$169	$58	$111
Total benefit			
QALYs	3.4386	2.9810	0.4577
LYs	4.8739	4.2416	0.6323
PFLYs	2.3210	1.5810	0.7401
ICER (QALY)	—	—	$197 667
ICER (LY)	—	—	$143, 080

Abbreviations: AE, adverse event; ET, endocrine therapy; ICER, incremental cost-effectiveness ratio; LY, life-year; PFLY, progression free life year; QALY, quality-adjusted life year; SGD, Singapore Dollar.
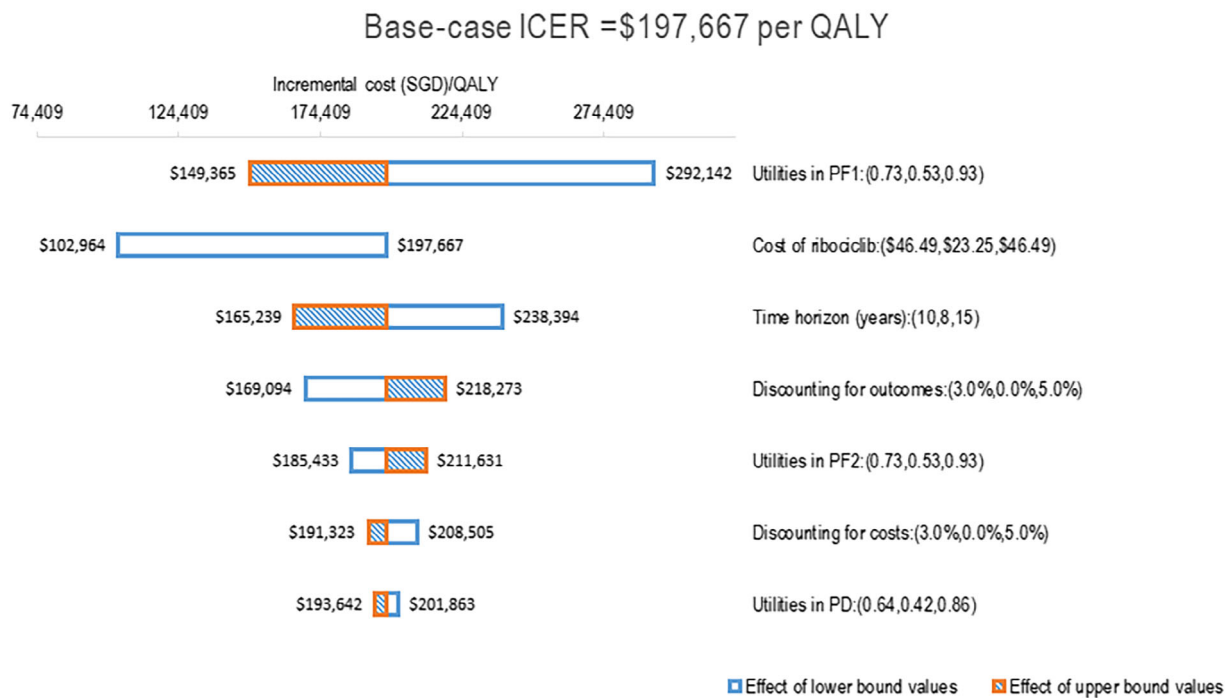
FIGURE 1 Tornado diagram of OWSA of the effect of the seven most influential variables on the cost effectiveness results of ribociclib plus endocrine therapy verses placebo plus endocrine therapy. Vertical axis represents the base-case ICER while the horizontal axis represents the change in ICER relative to base case for variables subjected to OWSA. Numbers in brackets represent the deterministic value of each parameter, followed by the lower and upper bounds of the value used in the OWSA. PD, progressed disease on second and subsequent lines of treatment; PF1, progression-free state on first-line treatment; PF2, progression-free state on second-line treatment

A probabilistic sensitivity analysis (PSA) was performed to explore the uncertainty of input parameters through random sampling from assigned distributions. Probability distributions were selected according to the nature of the variable. HSUVs were assumed to follow a beta distribution while survival functions for PFS and OS were sampled from a multivariate normal distribution via the Cholesky decomposition matrix.[28] Drug costs and cost of routine clinical care (ie, medical consultation visits, laboratory tests, etc.) were assumed to be certain and thus not varied in the PSA. Monte Carlo iterations were repeated over 15 000 iterations to generate an ICER distribution in a scatterplot. In addition, a cost-effectiveness acceptability curve (CEAC) was obtained showing the probability of cost-effectiveness of both treatments over a range of hypothetical willingness-to-pay (WTP) thresholds.

3 | RESULTS

3.1 | Base-case analysis

The base-case analysis over a time horizon of 10 years showed that adding ribociclib to goserelin and an aromatase inhibitor or tamoxifen

Cost-Effectiveness Acceptability Curve (CEAC)
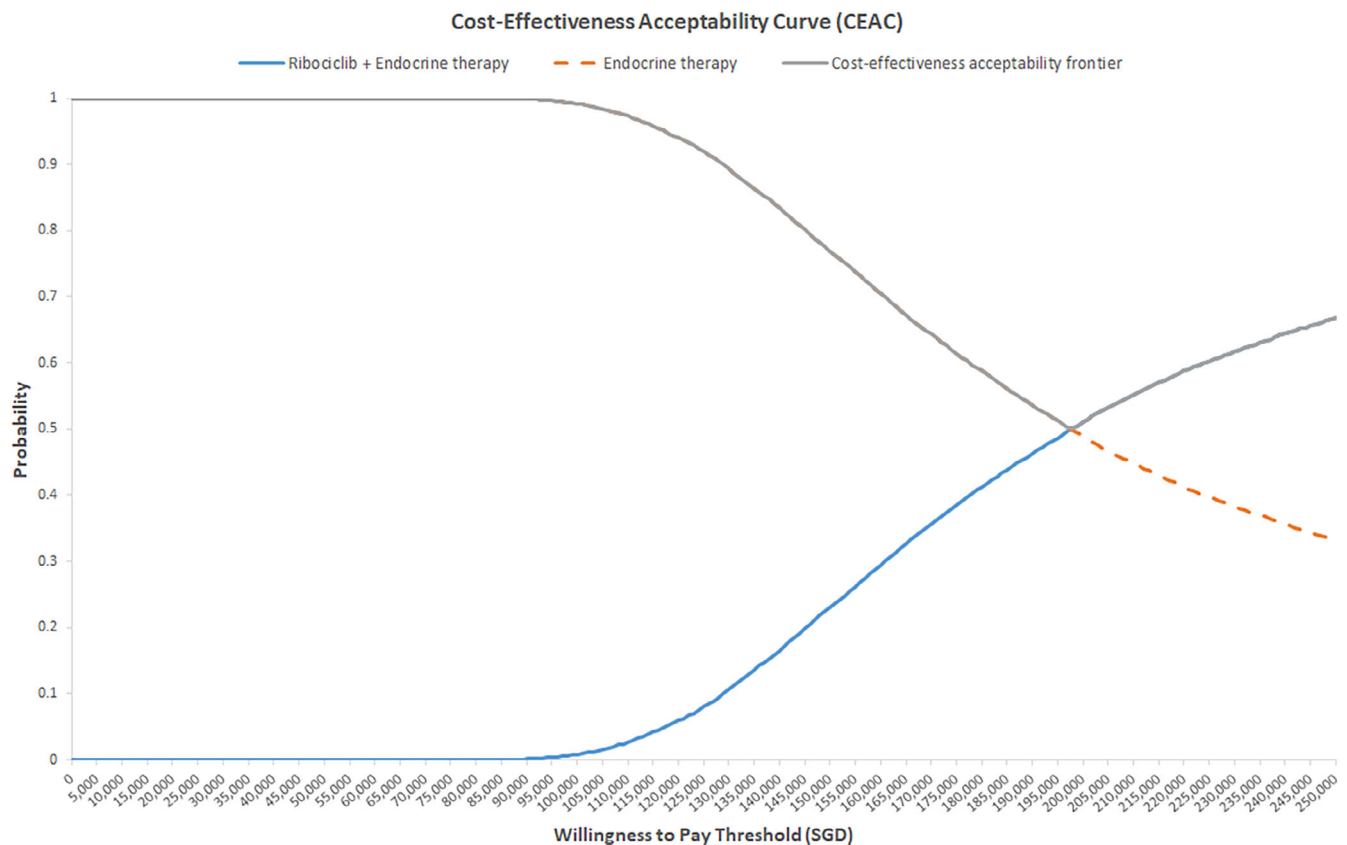
FIGURE 2 Cost-effectiveness acceptability curve for PSA

increased both effectiveness and costs, resulting in an ICER of SGD197,667/QALY and SGD143,080/LY gained (Table 2).

3.2 | Sensitivity analyses

OWSA confirmed that the ICER was most sensitive to the utilities in PF1, followed by the cost of ribociclib (Figure 1). The Tornado diagram showed that there were no instances whereby the ICER fell below SGD100,000/QALY gained except when the cost of ribociclib was reduced. The ICER remained unfavorably high across the range of possible model parameter values assumed.

Results from the PSA simulation were congruent with the base-case analysis demonstrating that adding ribociclib to ET was consistently more effective and costlier than ET alone. The mean ICER for ribociclib plus ET was marginally higher than the base-case ICER at SGD199,918/QALY gained. The CEAC showed that ribociclib had zero probability of being cost-effective when the WTP threshold was below SGD198,000/QALY (Figure 2).

3.3 | Scenario analyses

Additional scenario analyses were performed to examine how base-case assumptions affected the ICER (Table 3). In the absence of any

price reduction for ribociclib, all scenario analyses showed exceedingly high ICERs. Even with a 50% reduction in the price of ribociclib, the ICER remained high at SGD102,964/QALY. Applying a log-logistic parametric fit to the ribociclib OS curve and extending the time horizon to 15 years produced lower ICERs compared to the base-case scenario and using local HSUVs and limiting the treatment effect of ribociclib resulted in higher ICERs (Table 3). Changing the treatment mix for second and subsequent lines of therapy based on local treatment patterns had a significant impact on the ICER, potentially reducing the ICER to SGD111,066/ QALY. Given the high proportion of patients switching to palbociclib after disease progression in the comparator arm and the significantly higher list prices of palbociclib and abemaciclib than ribociclib, the local treatment scenario was also modeled using a single price across all CDK4/6 inhibitors, resulting in an ICER of SGD140,102/QALY.

4 | DISCUSSION

To our best knowledge, this is the first study addressing the cost-effectiveness of a CDK4/6 inhibitor for HR+, HER2− ABC in Singapore. Although MONALEESA-7 demonstrated a significant OS benefit with the addition of ribociclib to first-line ET in premenopausal women, our analyses revealed that this treatment combination does not represent a cost-effective use of healthcare resources at its

TABLE 3 Summary of cost and benefit in the scenario analyses

	Cost (SGD)	QALYs	LYs	PFLYs	ICER (SGD/QALY)
Base case					
Ribociclib + ET	**177 589**	**3.4386**	**4.8739**	**2.3210**	**197, 667**
ET alone	**87 119**	**2.9810**	**4.2416**	**1.5810**	
Survival curve parametric fit					
Log-logistic fit (OS ribociclib arm)					
Ribociclib + ET	184 474	3.7008	5.2836	2.3210	135 238
ET alone	87 119	2.9810	4.2416	1.5810	
Time horizon (15 years)					
Ribociclib + ET	183 303	3.6206	5.1528	2.3314	165 239
ET alone	90 051	3.0562	4.3582	1.5831	
Utility weights reference source					
Utilities from Tan et al.					
Ribociclib + ET	177 589	2.2782	4.8739	2.3210	210 488
ET alone	87 119	1.8484	4.2416	1.5810	
Ribociclib treatment effect					
Limit to 5 years					
Ribociclib + ET	174 716	3.3295	4.7035	2.3210	251 289
ET alone	87 119	2.9810	4.2416	1.5810	
Limit to 7 years					
Ribociclib + ET	176 643	3.4010	4.8151	2.3210	213 133
ET alone	87 119	2.9810	4.2416	1.5810	
Second and subsequent lines of treatment					
Local treatment algorithm (using list prices for CDK4/6 inhibitors)					
Ribociclib + ET	205 388	3.4386	4.8739	2.3210	111 066
ET alone	154 554	2.9810	4.2416	1.5810	
Local treatment algorithm (using a single price[a] across all CDK4/6 inhibitors)					
Ribociclib + ET	203 086	3.4386	4.8739	2.3210	140 102
ET alone	138 963	2.9810	4.2416	1.5810	
Pricing scenario					
25% price reduction					
Ribociclib + ET	155 495	3.4386	4.8739	2.3210	150 316
ET alone	86 697	2.9810	4.2416	1.5810	
50% price reduction					
Ribociclib + ET	133 401	3.4386	4.8739	2.3210	102 964
ET alone	86 276	2.9810	4.2416	1.5810	
75% price reduction					
Ribociclib + ET	111 307	3.4386	4.8739	2.3210	55 612
ET alone	85 854	2.9810	4.2416	1.5810	

Abbreviations: ET, endocrine therapy; ICER, incremental cost-effectiveness ratio; LY, life-year; OS, overall survival; PFLY, progression free life year; QALY, quality-adjusted life year; SGD, Singapore Dollar.
[a]The list price of ribociclib was used across all CDK4/6 inhibitors.

current price. There may be several reasons for this. Firstly, the lifetime drug cost per patient in the PF1 health state was SGD122,887 for ribociclib with ET compared to SGD21,961 for ET alone. The high ICER was primarily driven by the longer PFS in the ribociclib arm and the large cost difference between ribociclib (SGD2,929) and ET (SGD2 and SGD10 for tamoxifen and letrozole, respectively) for each 28-day cycle, resulting in high incremental costs. Secondly, on close examination, the OS curves of both treatment arms in MONALEESA-7 were quite similar up until 2 years, after which, they began to diverge. Consequently, despite the statistically significant OS

benefit, the magnitude of the modeled survival gain was insufficient to produce a favorable ICER.

OWSA assessing model key drivers revealed that the ICER was most sensitive to the HSUVs for the PF1 health state. As HSUVs were not directly available from the trial, an indirect method was used to estimate the QALYs in the model. Base-case HSUVs were obtained from a published Canadian quality of life study in patients with HR+, HER2− ABC where the EQ-5D questionnaire was used to derive utilities. EQ-5D is a preferred instrument for utility elicitation by several HTA agencies[21,22] and has often been used in breast cancer[29] and local CEAs.[30-32] As a generic measure, EQ-5D is better suited for health policy decisions and funding allocation as it allows for comparisons across disease areas and health technologies. As country settings may affect HSUVs, a scenario analysis was conducted based on local HSUVs[19] which resulted in a significantly higher ICER driven by lower local HSUVs in the PF1 health state.

Our base-case model had a time horizon of 10 years, which was lower than other published CEAs which used 15- to 40-year time horizons.[9-11] A 10-year time horizon was selected as the local 5-year survival rate for stage IV breast cancer was 27%. A longer time horizon than 10 years would have increased the model uncertainty as only 3 years of trial data was available and the model would have largely been based on extrapolation. A scenario analysis using a 15-year time horizon reduced the ICER to SGD165,239/QALY.

The PSA generated a similarly high ICER as the base case. The CEAC demonstrated that for a WTP threshold of up to SGD198,000/QALY, ET alone was the more cost-effective treatment option. While Singapore does not have an explicit WTP threshold to determine whether a drug represents good value for money, the wide variation in the upper and lower limits of the high base-case ICER from sensitivity and scenario analyses provides a strong indication that the addition of ribociclib is unlikely to represent a cost-effective treatment option in the local context.

Our results are comparable with overseas cost-effectiveness studies which found palbociclib or ribociclib were not cost-effective in the first-line setting, with ICERs ranging between USD100,000-770 000/QALY.[9-13] We did not compare the cost-effectiveness of ribociclib with other CDK4/6 inhibitors but several studies have reported that ribociclib is either cost-saving or cost-effective compared to palbociclib.[12,33] Of note, as none of the phase 3, first-line CDK4/6 inhibitor studies have reported mature OS results, all published CEAs were either based on immature OS data or data from, a small phase 2 trial which did not show an OS benefit.

For patients whose disease progress on ET, there is a lack of data on the most effective treatment pathway leading to highly variable treatment strategies. We used the subsequent treatments reported in MONALEESA-7 to calculate treatment costs in the base case and modified the treatment mix in a scenario analysis based on local clinician input. Changing the treatment mix had a significant impact on the overall ICER, reducing it by over SGD80,000/QALY. The higher proportion of patients receiving high-cost second and subsequent line treatments (eg, CDK4/6 inhibitors, olaparib, or alpelisib) in the comparator arm in the local setting vs MONALEESA-7 could have led to this difference. Notably, the list prices for palbociclib and abemaciclib were significantly higher than for ribociclib. When these prices were lowered to match the price of ribociclib, the ICER in the local setting increased by almost SGD30,000/QALY. Given the high variability in treatment strategies and drug prices, the generated ICER based on local treatment mix is highly uncertain.

Our analysis has several limitations. Firstly, about 30% of women in MONALEESA-7 did not receive second-line treatment which is unlike the local setting where only about 5% of patients do not proceed to second-line therapy. In addition, only 20% of women in the placebo arm received subsequent treatment with a CDK4/6 inhibitor, whereas local clinicians report up to 50% of patients who do not receive a CDK4/6 inhibitor as initial therapy, will receive one following progression. The impact of these differences on survival is unknown and although we modeled the impact of using local treatment mixes on treatment costs, we did not change the survival curves which were based on MONALEESA-7. Secondly, we extrapolated survival curves from available trial data of approximately 3 years to a 10-year time horizon and the uncertainty of this extrapolation is unknown. We examined the impact of using different parametric extrapolations on the ICER and limiting the treatment effect duration to 5 or 7 years. We explored the log-logistic distribution for the ribociclib OS curve as it had a good fit and lowest AIC. While this scenario favored ribociclib treatment, the ICER still remained above SGD100,000/QALY. As expected, limiting the treatment effect duration to 5 or 7 years increased the ICER. Thirdly, we used the average prices of drugs at PHIs which did not include discounts offered by the manufacturers to some patients through patient access schemes. As details of these schemes and the number of patients enrolled were not publicly available these discounts were not included in the model which could have overestimated treatment costs for some of the high-cost treatments used in the second or later line settings.

In conclusion, at its current list price, adding ribociclib to ET is unlikely to be cost-effective in Singapore when used in the first-line setting for HR+, HER2− premenopausal ABC. The similar efficacy of CDK4/6 inhibitors seen across trials suggests that their clinical effectiveness is comparable and independent of menopausal status. Therefore, palbociclib and abemaciclib are also unlikely to be cost-effective as they are priced higher than ribociclib. As CDK4/6 inhibitors are routinely used locally, results from this cost-effectiveness analysis will be useful to inform future value-based pricing discussions with manufacturers and national subsidy recommendations which also consider clinical effectiveness, safety and budget impact.

ETHICAL STATEMENT

Institutional ethics approval and patient consent were not required for this study.

AUTHOR CONTRIBUTIONS

Lydia Loke: Conceptualization; formal analysis; methodology; project administration; visualization; writing-original draft; writing-review and editing. **Soo Chin Lee:** Resources; validation; visualization; writing-review and editing. **Fiona Pearce:** Conceptualization; supervision; visualization; writing-review and editing. **Kwong Ng:** Conceptualization; supervision; visualization; writing-review and editing. **Mohamed Aziz:** Conceptualization; formal analysis; methodology; supervision; validation; visualization; writing-review and editing.

DATA AVAILABILITY STATEMENT

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.