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ORIGINAL RESEARCH ARTICLE

Cost Effectiveness of CDK4/6 Inhibitors in the First-Line Treatment of HR+/HER2− Metastatic Breast Cancer in Postmenopausal Women in the USA

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Abstract

Background and Objective Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors improve progression-free survival when combined with endocrine therapies in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. However, the comparative cost effectiveness of utilizing three US Food and Drug Administration-approved CDK4/6 inhibitors is unknown. Therefore, we aimed to evaluate the cost effectiveness of individual CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) with letrozole versus letrozole monotherapy in the first-line treatment of hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer in the USA.

Methods We constructed a Markov-based decision-analytic model to evaluate the cost effectiveness of CDK4/6 inhibitors plus endocrine therapies over a 40-year lifetime from a third-party payer perspective. The model incorporated health states (progression-free disease, progressive disease, and death), major adverse events (neutropenia), and cancer-specific and all-cause mortality. Using clinical efficacy and quality-of-life scores (utility) data from clinical trials, we estimated quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios using Medicare charges reported in US dollars per 2022 valuation and a discount rate of 3% applied to costs and outcomes. We performed deterministic and probabilistic sensitivity analyses to evaluate parametric and decision uncertainty.

Results Compared to letrozole, the model estimated an increase of 5.72, 5.87, and 6.39 in QALYs and costs of $799,178, $788,168, and $741,102 in combining palbociclib, ribociclib, and abemaciclib plus letrozole, respectively. Palbociclib or ribociclib plus letrozole were dominated by abemaciclib plus letrozole. Compared with letrozole, abemaciclib plus letrozole resulted in an incremental cost-effectiveness ratio of $457,538 per QALY with an incremental cost of $553,621 and an incremental QALY gain of 1.21. The results were sensitive to the cost of abemaciclib, disease progression utility, and patients' age.

Conclusions At a willingness to pay of $100,000/QALY gained, our model predicts that combining CDK4/6 inhibitors plus letrozole is not cost effective with a marginal increase in QALYs at a high cost. Lowering the cost of these drugs or identifying patients who can receive maximal benefit from CDK4/6 inhibitors would improve the value of this regimen in patients.

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1 Introduction

Despite significant developments in the diagnosis and management of early breast cancer, about one-third of patients still progress to stage IV metastatic breast cancer (MBC) [1]. Hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2−) disease comprises 65–70% of all patients with MBC [1]. There are over 100,000 women in the USA living with HR+/HER2− MBC, who have a median survival of only 2–3 years [2–4]. The prognosis of patients with HR+/HER2− MBC depends on

Key Points for Decision Makers

This is the first study to assess the cost effectiveness of all three US Food and Drug Administration-approved cyclin-dependent kinase 4 and 6 inhibitors in combination with the letrozole versus letrozole monotherapy from a US third-party payer perspective.

Cyclin-dependent kinase 4 and 6 inhibitors plus letrozole at willingness to pay of $100,000 are not cost effective because of the high cost and a slight increase in quality-adjusted life-years compared with letrozole monotherapy.

Abemaciclib added to letrozole is found to be a better choice in terms of quality-adjusted life-years among all cyclin-dependent kinase 4 and 6 inhibitors.

the sensitivity to endocrine therapy [5]. In the metastatic setting, up to 50% of patients have de novo resistance to endocrine therapy and have the shortest survival; the remaining patients, who initially respond, eventually acquire endocrine resistance, leading to disease progression and eventually death [6, 7].

Recently, CDK4/6 inhibitors have shown to overcome de novo and acquired endocrine resistance and have emerged as a major advance in HR+/HER2− MBC [8–10]. They target the aberrant cell cycle, which is one of the hallmarks of cancer [11–13]. The cyclin D and CDK4/6 complex phosphorylates and inhibits retinoblastoma protein, a tumor suppressor that arrests the G1 to S phase progression of the cell cycle [14–16]. Three CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) in breast cancer treatment have been approved by the US Food and Drug Administration. Recent studies have observed improved survival and nearly doubled progression-free survival (PFS) when the inhibitors are combined with endocrine therapies, such as aromatase inhibitors or fulvestrant, in the first- or second-line treatment of HR+/HER2− MBC [17–22].

While adding CDK4/6 inhibitors to endocrine therapies in HR+/HER2− MBC is promising, these drugs are very expensive. The monthly cost of these agents ranges from $600 to $13,000 [19, 23]. Several studies have been conducted to determine the cost effectiveness of some CDK4/6 inhibitors and found that palbociclib plus letrozole and ribociclib plus letrozole were not cost effective in the first-line treatment of patients with MBC in the Singapore healthcare system, Swiss healthcare system, and the Spanish National Health System, and from a US payer perspective [23–30]. However, an economic assessment of all three CDK4/6 inhibitors plus letrozole has not been conducted for the payers and clinical decision makers in the USA. While providing health benefits, the use of CDK4/6 inhibitors versus letrozole monotherapy may increase drug and healthcare expenditure. Cautious use of healthcare resources needs to be assessed by comparing the effectiveness of these treatments and their total costs (drug plus adverse event [AE] management) and summarizing the incremental cost per unit of health gained. In this study, we evaluate the cost effectiveness of individual CDK4/6 inhibitors (palbociclib, ribociclib, or abemaciclib) plus letrozole versus letrozole monotherapy in the first-line treatment of HR+/HER2− MBC. This is the first study to conduct a pharmacoeconomic assessment of all three CDK4/6 inhibitors from the US payer perspective.

2 Methods

2.1 Model Structure

We developed a Markov-based state transition model (Electronic Supplementary Material [ESM]) using TreeAge Pro 2022 software (TreeAge, Williamstown, MA, USA) to evaluate the cost effectiveness of treatment with CDK4/6 inhibitors with letrozole or letrozole alone for postmenopausal women with HR+/HER2− MBC from a US third-party payer perspective. The model simulated the clinical course of women aged between 45 and 75 years and treated for HR+/HER2− MBC over the 40-year time horizon (Fig. 1). The model tracked the patients with HR+/HER2− MBC through three disease states—PFS, progressive disease (PD), and death—to match the treatment protocol of randomized controlled trials (PALOMA-2, MONALEESA-2, and MONARCH-3) [18–20]. The model also took grade 3 or 4 AEs of neutropenia, a major AE of CDK4/6 inhibitors, into account in the assessment of all treatment arms. Our base-case population comprised progression-free HR+/HER2− MBC. We used a 4-week cycle length to advance time in the model consistent with the treatment cycle of the patients in all clinical trials [palbociclib plus letrozole (palbociclib 125 mg daily for 21 days followed by 1 week off plus letrozole 2.5 mg daily); ribociclib plus letrozole (ribociclib 600 mg daily for 21 days followed by 1 week off plus letrozole 2.5 mg daily); abemaciclib plus letrozole (abemaciclib 150 mg twice daily during for 28 days plus letrozole 2.5 mg daily); or letrozole alone (letrozole 2.5 mg daily)] [18–20]. A half-cycle correction was applied to both costs and effectiveness to account for events and transitions occurring at any point during the cycle, not necessarily at the start or end of each cycle, as per standard guidelines [19, 23, 31]. At each cycle, patients could remain in the PFS state, progress to the PD state, experience grade 3 or grade 4 neutropenia, or die. We

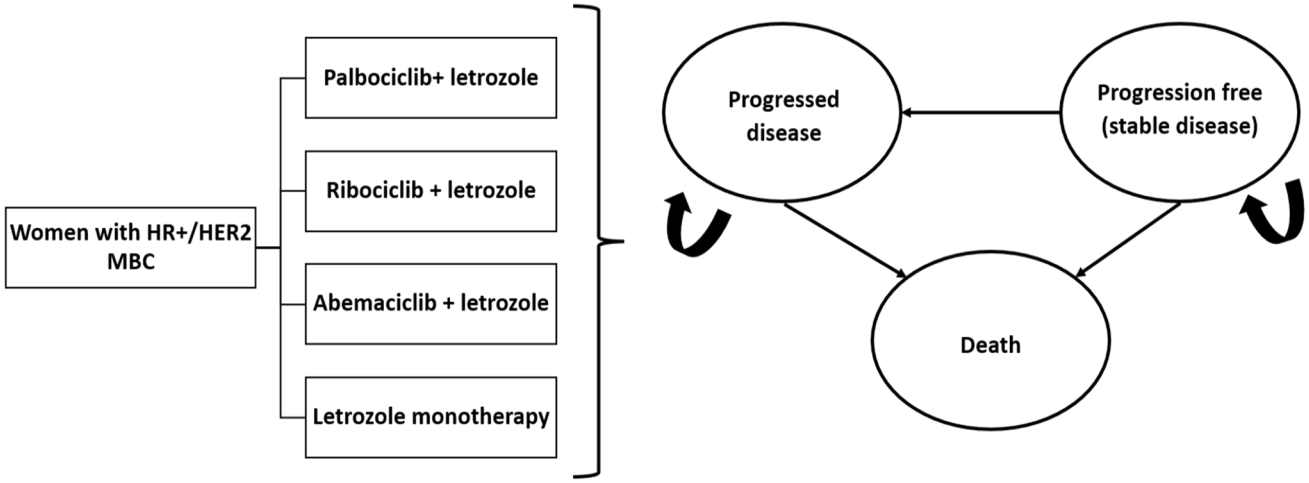

Fig. 1 Heath states in the model. Three states were considered in the model: progression free, progressed disease, and death. All patients started in the progression-free state and transitioned over time to progressed disease or death. Eventually, all subjects moved to the absorbing state, the death state. The *arrows* illustrate the directions of movements between different states. *HR+/HER2 MBC* hormone receptor-positive/ human epidermal growth factor receptor 2 metastatic breast cancer

calculated and calibrated transition probabilities to match the model results with the median overall survival (OS) observed in the clinical trials using a data-driven first-order Markovian method. The probability of patients experiencing a grade ≥ 3 neutropenia was derived from clinical studies [18–20].

2.2 Clinical Data

2.2.1 Efficacy

The clinical efficacy parameters in the model were derived from three clinical trials (PALOMA-2, MONALEESA-2, and MONARCH-3) [18–20]. These trials compared the efficacy and safety of CDK4/6 inhibitors with letrozole and letrozole monotherapy in patients with HR+/HER2− MBC. The effects of CDK4/6 inhibitor treatment were directly compared with the letrozole monotherapy group as a control. As MONARCH-3 included both letrozole and anastrozole as endocrine therapy, only letrozole data were used for our study (ESM).

2.2.2 PFS and OS

Progression-free survival and OS for palbociclib plus letrozole, ribociclib plus letrozole, and abemaciclib plus letrozole were obtained from the PALOMA-2, MONALEESA-2, and MONARCH 3, respectively. The patient population in these three trials comprised postmenopausal women with HR+/HER2− MBC who had not received prior treatment for advanced disease. They were comparable in terms of baseline characteristics such as median age, race, and disease stages [18–20]. In the absence of OS data for abemaciclib plus letrozole, we assumed that the OS rates of abemaciclib plus letrozole are similar to the OS rates of palbociclib plus letrozole [32] as both therapies share the same mechanism of action and have similar hazard ratios for the PFS benefit [19, 20]. Because of the limited follow-up time of the Kaplan–Meier curves in clinical trials, we extrapolated the PFS and OS rates by fitting the data to a distribution minimizing non-linear least squares. We tested exponential, Weibull, and log-normal distributions and selected exponential distribution based on the Akaike Information Criterion. The extrapolation of the Kaplan–Meier curves is represented in the ESM.

2.2.3 Health Benefits

The assessment of health benefits in the model was presented as the quality-adjusted life-year (QALY) gained.

2.2.4 Utility

Utility values used in the model were obtained from the large clinical trials PALOMA-2, MONALEESA-2, and MONARCH-3 [18–20] evaluating the health outcomes of combining palbociclib, ribociclib, and abemaciclib with letrozole, respectively. The utilities were derived from EQ-5D-5L data collected in PALOMA-2, MONALEESA-2, and MONARCH-3 as described before using the standard gamble technique [33] and from data identified through a literature review [19, 23, 29]. The units were sourced from

publicly available tariffs in the USA. [34] Key model parameters are presented in Table 1. All treatment and health state-specific utility weights were estimated from previously published studies [33, 35–37]. The impact of AEs on the utility values of the population was obtained from the literature [38]. The duration of AEs was derived from the published literature [34]. To evaluate the number of QALYs for each drug, health state utility (HSU) values are needed to weigh the time spent alive in each health state. The utility values were applied to the PFS and PD health states and the disutility values (1-HSU) were associated with AEs and the mean AE duration. The utility for a patient in the death state was considered the same for all treatment arms (Table 1). In addition, the age-specific differential quality-of-life units were obtained from a published report [39] (ESM).

2.3 Costs

As the model was developed from the US payer perspective, only the direct medical care costs including drug acquisition, administration, and management of AEs, hospitalization, and end-of-life care were considered. Patient transitions and length of stay among the PFS, PD, and death states were used to calculate the expected costs and effectiveness of treatment over a 40-year lifetime horizon. Drug costs were obtained using the Centers for Medicare & Medicaid Services [45]. All costs were inflated to 2022 dollars using the Consumer Price Index for Medical Care [46]. We also considered the costs associated with managing AEs and end-of-life care. The costs of treating severe neutropenia and associated disutility were included. The costs of end-of-life care for patients in a PD state were included. They were calculated by multiplying the cost in each cycle by the number of cycles and related costs were derived from the published literature. The monthly treatment costs were incurred only until the patient remained in the progression-free state. If a patient entered the progressed state, the costs did not continue. As patients often discontinue treatment before disease progression [18], the costs of CDK 4/6 inhibitors were modeled independently of PFS. Table 2 provides an overview of all costs and AE probabilities. The model provided several clinical and economic outcomes including the total cost, QALY, and incremental cost-effectiveness ratio (ICER). We assessed the cost effectiveness of the three combination treatment options with letrozole monotherapy using the following willingness-to-pay (WTP) threshold of $100,000 per QALY for the USA [47]. The WTP is a dollar value a payer is willing to pay for 1 QALY, $100,000 per QALY is a conventional WTP threshold used for the US payer perspective based on the economy. An annual discount

Table 1 Input parameters for the cost-effectiveness analysis (utilities and transition probabilities)

Resource item	Value [range]	Distribution	Source
Health state utilities (yearly)			
Progression-free	0.85 [0.64, 1.00]	β [15, 2.65]	Delea et al. [35]
Progressive disease	0.52 [0.39, 0.65]	β [48, 44.31]	Tengs et al. [40]
Death	0	–	
Neutropenia	0.15 [0.11, 0.19]	β [85, 481.67]	Lloyd et al. [33]
Disease progression (monthly probabilities)			
Palbociclib + letrozole	3.4% [2.6%, 4.3%]	β [17, 214]	PALOMA-2 [41]
Ribociclib + letrozole	2.7% [2.0%, 3.4%]	β [13, 207]	MONALEESA-2 [42]
Abemaciclib + letrozole	4.1% [2.8%, 5.4%]	β [19. 130]	MONARCH-3 [19]
Letrozole	6.6% [5.0%, 8.3%]	β [22, 387]	PALOMA-2
Death (monthly probabilities)			
Palbociclib + letrozole	1.38% [1.12%, 2.48%]	β [31, 34]	PALOMA-2 [32]
Ribociclib + letrozole	0.98% [0.79%, 1.01%]	β [17, 23]	MONALEESA-2 [43]
Abemaciclib + letrozole	1.38% [1.12, 2.48%]	β [31, 34]	MONARCH-3, PALOMA-2 [19, 32]
Letrozole	1.68% [1.11%, 1.37%]	β [17, 29]	PALOMA-2 [32]
Severe neutropenia (lifetime probabilities)			
Palbociclib + letrozole	54% [40.5%, 67.5%]	β [64, 19]	PALOMA-2 [41]
Ribociclib + letrozole	59% [44.3%, 73.8%]	β [71, 23]	MONALEESA-2 [42]
Abemaciclib + letrozole	41.3% [30.4%, 56.1%]	β [84,11]	MONARCH-3 [19]
Letrozole	1.1% [0.8%, 1.4%]	β [17, 63]	PALOMA-2 [41]
Disutilities of severe neutropenia (yearly)	0.25 [0.27, 0.22]	Constant	Beauchemin et al. [44]

Table 2 Input parameters for the cost-effectiveness analysis (costs)

Resource item	Daily dose (mg)	Monthly dose (mg)	Cost (US$)/month	Distributions		Source
Drug costs						
Palbociclib	125	2625	14,108 [11,286, 16,930]	γ (100,88)		CMS drug prices [45]
Ribociclib	600	12,600	16,511 [132,208, 19,183]	γ (100, 0.22)		
Abemaciclib	300	8400	7024 [5619, 8,423, 7,373]	γ (100,31)		
Letrozole	2.5	70	802 [646, 969]	γ (100, 19)		
Resource item	Frequency	Unit cost (US$)		Distributions		Source
		PF	PD	PF	PD	
Medical costs						
End-of-life care	One time	11,349	–	γ (191, 11)	–	[37]
Outpatient visit	Once monthly	59	267	γ (38,6)	γ (66,17)	[34, 46]
Bone metastases management	Once monthly	202	429	γ (3,59)	γ (17,87)	[34, 46]
Hospitalization	Once monthly	342	883	γ (41,9)	γ (56,11)	[34, 46]
Monitoring (LFT, CBC, and CMP)	Once monthly	18	–	γ (12, 6)	–	[34, 46]
Laboratory scan and tests	Once monthly	–	528	–	γ (12,2)	[34, 46]
Bone scan	Once monthly	67	–	γ (3, 59)	–	[34, 46]
CT scan	Once monthly	174	–	γ (18, 34)	–	[34, 46]
AE costs						
Severe neutropenia	One time	7818 [3325, 5541]		γ (1322, 22)		[36]

CBC complete blood count, *CMP* comprehensive metabolic panel, *CMS* Centers for Medicare & Medicaid Services, *CT* computerized tomography, *LFT* liver function test, *PF* progression free, *PD* progressed disease

rate of 3% was applied to both costs and QALYs [48]. A cost distribution worksheet was developed, including the relevant cost measures (Table 2).

2.4 Sensitivity Analyses

A series of one-way deterministic sensitivity analyses was performed to determine key drivers of costs and effectiveness. Deterministic sensitivity analyses were performed around discount rates (1.5 and 6% per annum for both future costs and outcomes compared with 3% per annum in the base case), time horizons (5 years and 15 years compared with 40 years in the base case), as well as treatments and costs (± 20%). In the univariate sensitivity analysis, the parameters with the greatest influence on the ICER at a WTP of $100,000 were presented using a tornado diagram. For the probabilistic sensitivity analysis (PSA), the key parameters included clinical, cost, and utility data. We performed the PSA using 10,000 samples of the parameters obtained using the Monte-Carlo simulation [49]. To conduct a PSA, probabilistic distributions chose the recommendations outlined in handbooks of health economic evaluations were assigned to each input in the model and used to randomly select new plausible values [50]. Our study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guidance [51].

2.5 Model Validation

The validity of the model was assessed using the Assessment of the Validation Status of Health-Economic Decision Models Checklist [52]. A clinical expert reviewed the assumptions, model structure, and results. Independent checks were undertaken in the TreeAge sheets to detect any modeling errors to emphasize the face validity of the modeling approach and data sources. Validation efforts comprised running the model with extreme sets of parameter values to identify coding errors, checking that the sum of Markov state probabilities was always equal to 1. The external validity of the predicted outcomes compared with other published studies [23].

3 Results

In the base-case analysis for the overall cohort of HR+/HER2− MBC, treatment with abemaciclib plus letrozole was associated with an incremental gain of 1.21 QALYs relative to the use of letrozole alone (6.39 QALYs for abemaciclib plus letrozole vs 5.18 QALYs for letrozole alone). However, total healthcare costs were also higher for the abemaciclib plus letrozole arm ($741,102, for abemaciclib plus letrozole versus $187,481 for letrozole) resulting in an ICER of $512,612 per QALY gained for abemaciclib plus letrozole versus letrozole alone. The total healthcare costs

for palbociclib plus letrozole and ribociclib plus letrozole were $799,178 and $788,168, respectively. In terms of incremental QALYs, palbociclib plus letrozole and ribociclib plus letrozole were associated with higher costs and lower QALYs (dominated strategies), compared with abemaciclib plus letrozole and letrozole alone (Table 3). Abemaciclib plus letrozole provided an additional 3.11 life-years with an incremental cost of $604,632 as compared with letrozole alone (undiscounted) [ESM].

Sensitivity analyses confirmed the base-case analysis. Cost of abemaciclib, disease progression utility, and patients' age were key model drivers (Fig. 2).

Table 3 Summary of the cost-effectiveness analysis

Strategy	Cost, $US	QALYs	ICER ($US/QALY)
Letrozole	187,481	5.18	Reference
Abemaciclib + letrozole	741,102	6.39	$457,538
Ribociclib + letrozole	788,168	5.87	Dominated
Palbociclib + letrozole	799,178	5.72	Dominated

ICER incremental cost-effectiveness ratio, *QALYs* quality-adjusted life-years

Changes in discount rates and time horizons influenced the findings of the study as expected. Decreasing the time horizon to 5 years increased the ICER to $1,576,562 per QALY gained and 15 years resulted in the ICER increased to $799,283 per QALY gained. Decreasing the discount rate to 1.5% per annum (compared with 3% per annum in the base case) led to an ICER of $694,169 per QALY gained while increasing it to 6% per annum resulted in the ICER increasing to $913,753 per QALY gained for abemaciclib plus letrozole versus letrozole alone. According to the PSA, abemaciclib plus letrozole was associated with an incremental cost of US$478,985 and an incremental QALY gain of 1.21, with an ICER of US$395,856 per QALY gained compared with letrozole. The probabilities that abemaciclib plus letrozole were cost effective versus letrozole monotherapy at thresholds of $50,000, $100,000, and $200,000 per QALY gained were 0% (ESM).

4 Discussion

In this study, the cost effectiveness of three Food and Drug Administration-approved CDK4/6 inhibitors combined with letrozole was estimated in the first-line treatment of

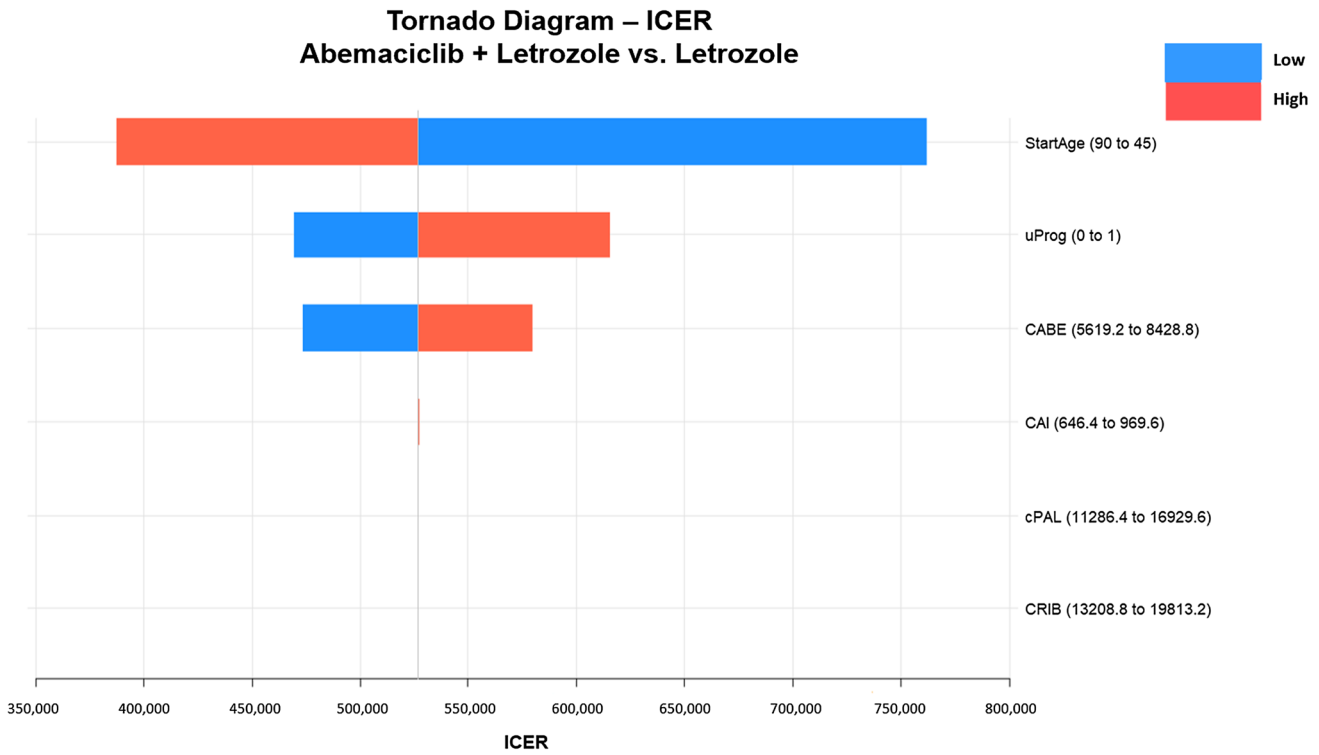

Fig. 2 Sensitivity analyses, tornado diagram. One-way sensitivity analysis of treatment strategies for hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. Tornado diagrams showing uncertainty from model inputs of US payer perspectives. *CABE* cost of abemaciclib, *CAI* cost of letrozole, *cPAL Cost of Palbociclib*, *CRIB Cost of Ribociclib*, *ICER* incremental cost-effectiveness ratio, *StartAge* age of patient initiating treatment, *uProg* utility of disease progression

women with HR+/HER2− MBC. The current analysis is one of the first cost-effectiveness analyses of abemaciclib plus letrozole compared to other CDK4/6 inhibitors in the first-line treatment of women with HR+/HER2− MBC for the USA. Although combining CDK4/6 inhibitors with letrozole therapy increased QALYs of patients with HR+/HER2− MBC, none of the CDK4/6 inhibitors was cost effective, suggesting letrozole monotherapy as the most cost-effective option among these four interventions at a WTP threshold of $100,000 per QALY gained. Among three CDK4/6 inhibitors, abemaciclib (plus letrozole) dominated the other two in terms of both cost and QALYs. When compared with letrozole monotherapy, abemaciclib plus letrozole resulted in an ICER of $457,538 per QALY, which was beyond the WTP for the USA. These results may inform formulary decision making and therapeutic selection for individual patients in clinical practice. Letrozole remains an optimal choice after considering the cost to QALYs; however, the cost is more than the WTP threshold of $100,000 per QALY gained.

Ours is the only cost-effectiveness analysis of abemaciclib plus letrozole in the first-line setting published to date. Our findings are broadly consistent with previous studies reporting the lack of cost effectiveness of palbociclib plus letrozole and ribociclib plus letrozole at current drug prices in the USA. [23, 24, 26, 47]. Although not cost effective, the addition of abemaciclib is more favorable than other CDK4/6 inhibitors to letrozole because of higher QALYs. While there are no head-to-head clinical comparisons for different CDK4/6 inhibitors, abemaciclib has better potency for inhibiting CDK4 and CDK6 compared with palbociclib and ribociclib [15, 27, 53–55]. Additionally, a continuous daily regimen of abemaciclib is thought to be beneficial in causing a sustained inhibition of CDK4 and CDK6 in contrast with the intermittent dosing of palbociclib and ribociclib [55–57]. Even if we assume no significant differences in clinical response among the three CDK4/6 inhibitors, as suggested by a recent meta-analysis evaluating their combinations with fulvestrant [58], the better cost effectiveness may make abemaciclib an overall favorable choice for the hospital formulary. However, the toxicity profile of CDK4/6 inhibitors must be taken into consideration before making a treatment decision for each patient individually.

Our study has several strengths. First, the main data sources were PALOMA-2, MONALEESA-2, and MONARCH-3 that enrolled patients from the USA and other global sites[18–20]. The cost of CDK4/6 inhibitors treatment was also directly modeled from exposure trial data, which provided a reasonable prediction of drug costs [23, 59]. Our analysis was based on reasonable assumptions and adhered to the recommendations to perform a cost-effectiveness analysis [60]. This is one of the first studies that has modeled all the CDK4/6 inhibitors used in the treatment for MBC. Furthermore, the sensitivity analyses were carried out to assess the impact of uncertainty on the results. Our deterministic sensitivity analyses revealed that the cost of abemaciclib, disease progression utility, and patients' age had the greatest effects on our findings. The cost and utility of disease progression in our model were derived from the literature, which may limit the accuracy of our results. The estimated ICER for abemaciclib plus letrozole versus letrozole alone was however over $600,000/QALY, when the disease progression utility was adjusted to the lower and upper values, implying that the effects of the disease progression utility scores on the long-term results were modest between the two treatment arms. In the PSA, there was a 0% probability that abemaciclib plus letrozole was cost effective compared to letrozole monotherapy at thresholds of $50,000, $100,000, and $200,000 per QALY gained. Our findings are consistent with some published studies that have already evaluated the cost effectiveness of palbociclib and ribociclib with letrozole in the USA. [23, 34]. These studies had a common inference that when CDK4/6 inhibitors were added to endocrine therapy, they were not a cost-effective choice at current drug prices in the USA. However, CDK4/6 inhibitors are found to be cost effective in Canada [61, 62], largely owing to the lower cost of these agents. Our model validation in comparison to the Zhang and Long study gave similar results, the addition of a CDK4/6 inhibitor to letrozole was not cost effective in the USA at a WTP of $100,000 per QALY [23].

Our study has some limitations. The data from separate clinical trials rely on the assumption that the sources are generalizable to each other, which may not hold true if one population is healthier than another or has better access to healthcare. The extent of any bias from the mixing of studies is unclear, given that this assumption applied to all strategies in the analysis. Our study considered the impact of only significant AEs on costs, which may have led to calculated total costs lower than those in clinical practice. Further research including the costs of all AEs in US patients with postmenopausal HR+/HER2− breast cancer would help reduce uncertainty surrounding future evaluations in this area. In the model, we assumed that patients who progress will remain in a progression state until death. However, in real life, some of these patients might respond to subsequent lines of treatments and achieve prolonged remission. As OS data were not available for abemaciclib plus letrozole at the time of this analysis, we assumed equivalent OS to palbociclib plus letrozole because of the similar mechanism of action and hazard ratios in PFS benefit. Consistent with approaches used in previous literature [63], clinical efficacy

was based on OS extrapolated using exponential distributions (as considered by other cost-effectiveness analyses [63, 64]) to directly estimate the transition probability from progressed disease to death in the terminal Markov model. Therefore, the long-term benefit of CDK4/6 inhibitors was accounted for in our model even though the benefit of abemaciclib may not have been accurately captured because of the unavailability of OS data. Our approach could have also overestimated the costs, as we could not consider dose modifications in the model because the time for dose modifications in the treatment course was not specified in the clinical trials. Our analysis also may not reflect real-world outcomes and "real- world" cost effectiveness because we have used clinical trial data. Further, long-term consequences of combination/subsequent treatments cannot be modeled for non-progression states. In addition, further studies are needed to include the full social costs or benefits to the population as a whole because societal costs (such as lost resources as a consequence of absenteeism, costs of informal care) represent a huge economic burden and may change the results or the conclusion about the adoption of the assessed treatments. The unit costs assigned to all medications, health states, management of AEs, and monitoring were carried out from the US payer perspective. Hence, our study findings are generalizable to the US healthcare system only.

5 Conclusions

Based on the results of our cost-effectiveness analysis, none of the CDK4/6 inhibitors was cost effective compared to letrozole monotherapy in the first-line treatment of HR+/HER2− BC. However, abemaciclib plus letrozole was found to be a better choice in terms of QALYs, consistent with clinical trial findings that combination therapies are more effective in delaying disease progression and improving OS. In the USA, all the new oncology drugs have very high costs, and most are found to not be cost effective [65]. Therefore, there is a need for effective policies to find a balance between lowering US drug prices while sustaining robust research and development investments and not disrupting innovation [66]. As a reduction in the price by the pharmaceutical companies is unlikely [67], a better alternative is to increase the proportion of patients who respond to CDK4/6 inhibitors. De novo resistance is seen in 15–20% of patients and the objective response rate is less than 50% in the first-line setting using a combination of CDK4/6 inhibitors plus letrozole [18–20]. Novel predictive biomarkers that can help select patients who are more likely to derive clinical benefit from CDK4/6 inhibitors will spare others from toxicities and high costs. Novel OMICS technologies that use liquid biopsy samples should be utilized to develop and validate a panel of clinical biomarkers that predict response or resistance to CDK4/6 inhibitors in patients [67].

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Declarations

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Ethics Approval Data used for this study were publicly available; therefore, no ethics approval was required.

Consent to Participate Data used for this study were publicly available; therefore, no informed consent was required.

Consent for Publication Not applicable.

Availability of Data and Material All data used for this study are provided in the article or are publicly available. Additional details are available from the corresponding author on request.

Code Availability Not applicable.

Authors' Contributions PPM reviewed the literature, collected data, performed the analysis, and drafted the manuscript. AAD reviewed the study design, analysis, and manuscript. HD reviewed the analysis and manuscript. MVT conceived the study and supervised the literature review, data collection, and manuscript preparation. All authors read and approved the manuscript.

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