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BRIEF REPORT

Cost-effectiveness analysis of palbociclib or ribociclib in the treatment of advanced hormone receptor-positive, HER2-negative breast cancer

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Abstract

Purpose Three CDK4/6 inhibitors, palbociclib (PAL), ribociclib (RIB), and abemaciclib, when combined with letrozole (LET), have been approved as first-line therapy for postmenopausal women with metastatic HR+, HER2− breast cancer. However, an economic evaluation of these newer therapies is currently lacking. The purpose of this article is to evaluate the cost-effectiveness of PAL or RIB for the treatment of advanced HR+, HER2− breast cancer in the United States.

Methods A Markov simulation model was constructed using data from published clinical trials evaluating PAL and RIB. Three simulated treatment strategies included PAL + LET, RIB + LET, or LET alone. The main outcome measures were simulated progression-free survival (PFS), overall survival (OS), costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs).

Results Simulated median OS was 38.9 months for PAL + LET and 33.0 months for LET alone. Simulated median OS for RIB + LET was 43.3 months. Compared to LET alone, PAL + LET provided an additional 0.48 QALYs, on average, with an ICER of $634,000 per QALY gained; RIB + LET provided an additional 0.86 QALYs, on average, with an ICER of $440,000 per QALY gained. At current prices, neither PAL nor RIB was cost-effective, assuming a willingness-to-pay threshold of $100,000 per QALY gained. To reach such a cost-effectiveness threshold, PAL and RIB prices must decrease by approximately 70%.

Conclusion Despite significant gains in progression-free survival over letrozole alone, the addition of palbociclib or ribociclib in the treatment of advanced HR+, HER2− breast cancer is not cost-effective in the United States given current drug prices.

Keywords Cost-effective analysis · Palbociclib · Ribociclib · Letrozole · Advanced breast cancer · Hormone receptor positive

Introduction

A new drug class, cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors, augments endocrine therapy as standard of care for advanced hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) breast cancer. The first CDK4/6 inhibitor, palbociclib (PAL), gained accelerated approval in 2015 as first-line therapy for postmenopausal women with metastatic HR+, HER2− breast cancer. Ribociclib (RIB) and abemaciclib were subsequently approved for the same indication.

A phase II trial (PALOMA-1) of palbociclib among postmenopausal women with advanced HR+, HER2− breast cancer demonstrated a median progression-free survival (PFS) of 20.2 months in patients receiving PAL + LET (letrozole), a significant improvement over LET alone (PFS: 10.2 months; HR = 0.488, $p = 0.0004$) [1]. Median overall survival (OS) with PAL + LET was 37.5 months versus 34.5 months with LET alone (HR = 0.897, $p = 0.281$) [2]. A subsequent phase III trial (PALOMA-2) showed similar PFS, with OS data pending at this time. A phase III trial (MONALEESA-2) [3] of ribociclib demonstrated a median PFS of 25.3 months for RIB + LET versus 16.0 months for

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LET alone (HR = 0.568, $p < 0.0001$) [4]. Overall survival data are not yet available.

The most common side effect observed in patients taking palbociclib or ribociclib was severe neutropenia. In PALOMA-1, 54% of patients in the PAL + LET group developed severe neutropenia, compared to 1% on LET [1]. In MONALEESA-2, 59% of those receiving RIB + LET developed severe neutropenia versus 9% in the LET group [3].

Early improvements in PFS have demonstrated the efficacy of CDK4/6 inhibitors in patients with metastatic HR+, HER2− breast cancer. The high monthly cost of therapy, however, warrants further investigation into whether treatment with CDK4/6 inhibitors improves long-term quality-adjusted survival and is cost-effective.

Methods

We developed a Markov cohort model to simulate OS and PFS, beyond existing clinical trial follow-up periods, and to evaluate the cost-effectiveness of treatment with CDK4/6 inhibitors for postmenopausal women with advanced HR+, HER2− breast cancer. The model was implemented in TreeAge Pro® software.

Health states

A hypothetical cohort of 10,000 patients was assigned to follow one of three treatment strategies, in accordance with trial regimens: PAL + LET (palbociclib 125 mg daily for 21 days followed by 1 week off, plus letrozole 2.5 mg daily), RIB + LET (ribociclib 600 mg daily for 21 days followed by 1 week off, letrozole LET 2.5 mg daily), or LET alone (letrozole 2.5 mg daily). For each treatment arm, the Markov model consists of three mutually exclusive states: progression-free disease (PF), progressive disease (PD), and death. All patients begin in the PF state, and either stay in PF or transition to PD; patients then remain with PD or transition to death. Model cycle length is 4 weeks, consistent with a clinical treatment cycle. All simulated patients were tracked until eventual death.

We estimated disease progression or death rates using available PFS or OS data, respectively, as observed in the trials: PALOMA-1 for palbociclib, MONALEESA-2 for ribociclib (Table 1). Because OS data from MONALEESA-2 are not yet available, we used PALOMA-1 data to estimate death rates from PD for both PAL and RIB regimens. Constant hazard rates for disease progression were calculated as:

$$\text{Rate} = -\frac{\ln(1-0.5)}{\text{Median time until progression}}$$

Markov transition probabilities were computed as

$$\text{Probability} = 1 - e^{-\text{rate}\times t},$$

where t refers to a 1-month cycle. A similar approach was used to calculate the monthly probability of death.

Cost and utilities

Drug costs were obtained using Micromedex® RED BOOK Online® average wholesale prices. Health utilities were estimated from published studies (Table 1) [5–10]. The cost of treating severe neutropenia and associated disutility were included. All costs were converted to 2016 US dollars using the medical component of the consumer price index.

QALYs were computed by aggregating the total time spent in all health states, adjusted by the corresponding utility, until death. Incremental cost-effectiveness ratios (ICERs) were calculated as:

$$\text{ICER}_{\text{PAL+LET}} = \frac{\text{Cost}_{\text{PAL+LET}} - \text{Cost}_{\text{LET}}}{\text{QALY}_{\text{PAL+LET}} - \text{QALY}_{\text{LET}}}$$

$$\text{ICER}_{\text{RIB+LET}} = \frac{\text{Cost}_{\text{RIB+LET}} - \text{Cost}_{\text{LET}}}{\text{QALY}_{\text{RIB+LET}} - \text{QALY}_{\text{LET}}}.$$

ICERs were compared against a willingness-to-pay threshold of $100,000 per QALY gained. All costs and QALYs were discounted at a 3% annual rate.

Results

Model validation

Clinical outcomes of the Markov model were consistent with published clinical trial results (Fig. 1). Simulated median OS was 38.9 months for PAL + LET and 33.0 months for LET alone, similar to published OS in PALMOA-1 (37.5 months and 34.5 months, respectively). Simulated median OS for RIB + LET was 43.3 months; however, clinical trial data on RIB + LET OS remain unavailable at this time.

Cost-effectiveness analyses

Treatment with LET alone resulted in average lifetime costs of $170,829 and 2.08 QALYs. Adding PAL increased average lifetime costs to $475,339 and health benefits to 2.56 QALYs, resulting in an ICER of $634,000 per QALY gained. Treatment with RIB + LET resulted in average costs of $549,164 and 2.94 QALYs, leading to an ICER of $440,000 (Table 2, Supplemental Figure S1).

We used the simulation model to identify the prices at which palbociclib or ribociclib would reach a cost-effectiveness threshold of $100,000 per QALY gained. Palbociclib must decrease by 71% to $3800 per month, and

Table 1 Summary of model input parameters

Model parameter	Value	Range[b]	Source
Costs ($)			
Palbociclib (monthly)	13,155	[9866, 16,444]	RED BOOK Online®
Ribociclib (monthly)	13,140	[9855, 16,425]	RED BOOK Online®
Letrozole (monthly)	544	[408, 816]	RED BOOK Online®
Severe neutropenia	4,433	[3325, 5541]	Stokes et al. [8]
Follow-up treatment after disease progression (monthly)	6,786	[5090, 8482]	Xie et al. [10]
End-of-life care	9,032	[6774, 11,290]	Sorensen et al. [7]
Disease progression (monthly probability)			
Palbociclib + letrozole	3.4%	[2.6%, 4.3%]	Paloma-1 [1]
Ribociclib + letrozole	2.7%	[2.0%, 3.4%]	Monaleesa-2 [3]
Letrozole	6.6%	[5.0%, 8.3%]	Paloma-1 [1]
Death (monthly probability)			
Palbociclib + Letrozole	3.9%	[2.9%, 4.9%]	Paloma-1 [1]
Ribociclib + Letrozole	3.9%	[2.9%, 4.9%]	Model assumption
Letrozole	2.8%	[2.1%, 3.5%]	Paloma-1 [1]
Severe neutropenia (lifetime probability)			
Palbociclib + letrozole	54%	[40.5%, 67.5%]	Paloma-1 [1]
Ribociclib + letrozole	59%	[44.3%, 73.8%]	Monaleesa-2 [3]
Letrozole	1.1%	[0.8%, 1.4%]	Paloma-1, Monaleesa-2 [1, 3]
Health state utilities (yearly)			
Progression-free	0.85	[0.64, 1.00]	Delea et al. [5]
Progressive disease	0.52	[0.39, 0.65]	Tengs et al. [9]
Severe neutropenia[a]	Δ0.15	[0.11, 0.19]	Lloyd et al. [6]
Death	0	–	

[a]Severe neutropenia (defined as Common Terminology Criteria for Adverse Events grade 3 and above) utility was discounted from baseline utilities

[b]All parameters varied by ±25% on the original value, with utilities capped at 1

ribociclib must decrease by 67% to $4300 per month, in order to become cost-effective in this patient population. We performed univariate sensitivity analyses on all input parameters (Supplemental Figure S2).

Discussion

Recent clinical trials have demonstrated significant gains in PFS, and promising results in OS for women with metastatic HR+, HER2− breast cancer taking CDK4/6 inhibitors. Our simulation model demonstrates that neither palbociclib nor ribociclib are cost-effective at current drug prices.

Our findings are broadly consistent with previous studies that found that PAL was not cost-effective in the U.S [11] nor Switzerland [12]. Although not cost-effective at current prices, ribociclib is slightly more favorable than palbociclib because of prolonged PFS. One previous study compared the cost-effectiveness of palbociclib to ribociclib in the U.S. healthcare setting, and found that ribociclib was cost-effective with an ICER of $198,000, in part because the authors assumed more optimistic survival gains on ribociclib [13].

Our analysis has several limitations. We used currently available PALOMA-1 OS data to calculate PD to death transition probabilities for all treatment arms. Differences in the phase II PALOMA-1 and phase III MONALESSA-2 trials may exist, including the smaller enrollment of PALOMA-1. In the absence of available data on overall survival for the phase III PALOMA-2 trial, we performed additional sensitivity analyses on OS under the PAL + LET regimen (Supplemental Fig. 3). For example, if median OS with PAL + LET reached 50 months—nearly a 12-month gain over PALOMA-1 results—due to a slower rate of disease progression, the cost-effectiveness of PAL + LET still exceeds $350,000 per QALY gained compared to LET alone. Our analyses could be readily updated once OS data from PALOMA-2 and MONALEESA-2 trials become available. We did not consider other potential costs such as physician visits or hospital costs. We excluded abemaciclib from our

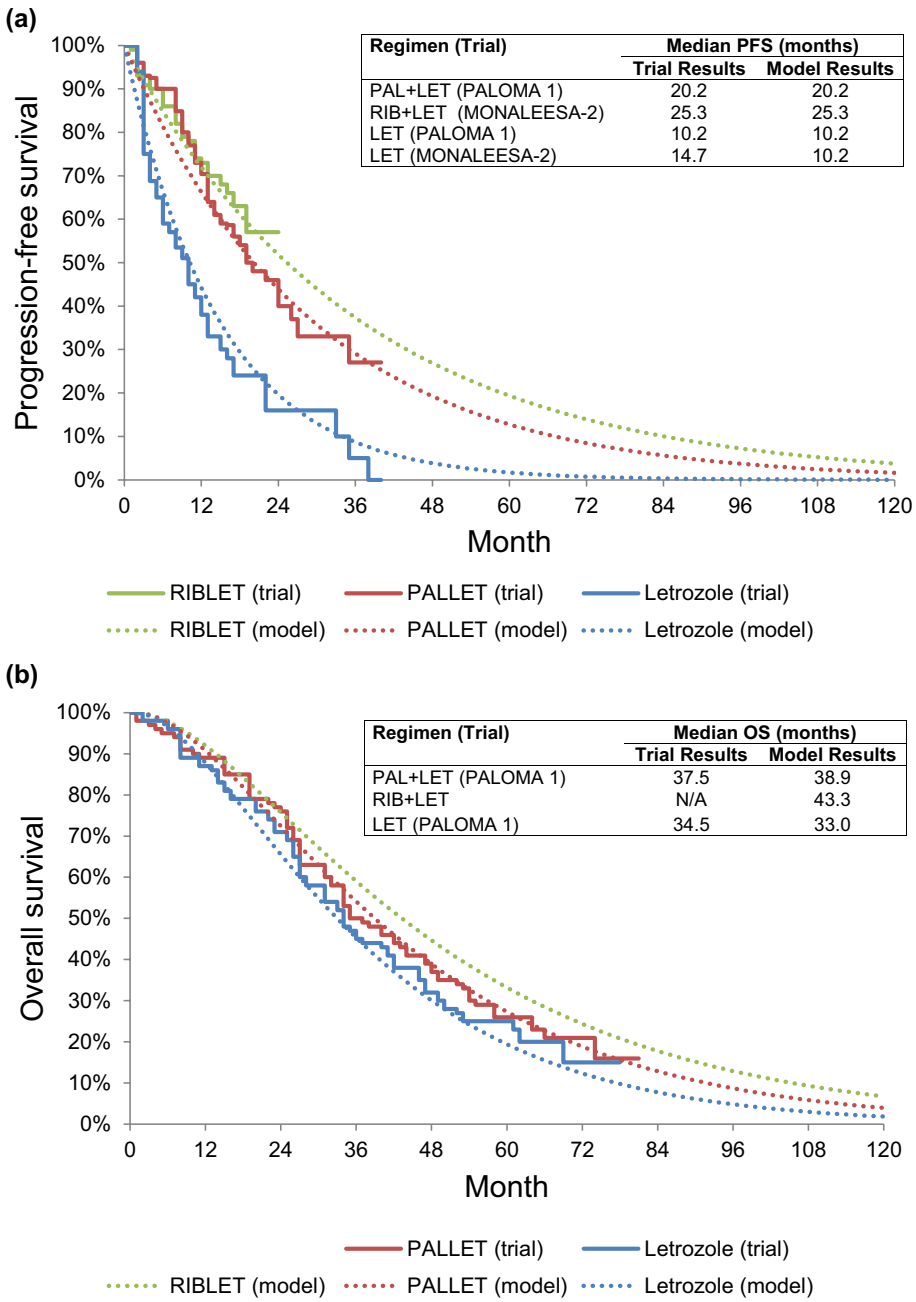

Fig. 1 Model validation to clinical trial data for **a** progression-free survival and **b** overall survival. Note: Overall survival data for RIB + LET are not yet available

analysis because trial data were not yet available; however, we could include this therapy in future analyses. An important difference of abemaciclib compared to palbociclib and ribociclib is that neutropenia was less frequently reported and thus, abemaciclib could be dosed continuously [14].

Conclusions

At current prices, neither palbociclib nor ribociclib for treating advanced breast cancer is cost-effective in the U.S. healthcare system. A recent study estimated that 155,000 women were living with metastatic breast cancer in the U.S. in 2017, of which approximately 70% of breast tumors are HR+ [15]. With more than 100,000 women living with metastatic breast cancer who are potential candidates for CDK4/6 inhibitors, the cost of treatment with these drugs could exceed $17 billion annually. Containing healthcare costs will likely require developing incentives to spur innovation. In 2017, the first CAR-T cell therapy, tisagenlecleucel (Kymriah®), received FDA approval but includes a steep price tag of $475,000 per treatment course. Its manufacturer is pursuing an "outcome based" pricing model with full reimbursement occurring only if patients respond after

Table 2 Cost-effectiveness analyses and scenarios with 25%, 50%, and 75% price reductions

Regimen	Lifetime costs ($)	Life expectancy (years)	Health benefits (QALYs)	ICER ($/QALY)
Letrozole	170,829	3.47	2.08	–
Palbociclib + letrozole (base price)	475,339	3.77	2.56	634,396
25% price reduction	385,444			447,115
50% price reduction	295,549			259,833
75% price reduction	205,653			72,550
Ribociclib + letrozole (base price)	549,164	4.27	2.94	439,924
25% price reduction	440,628			313,720
50% price reduction	332,093			187,516
75% price reduction	223,558			61,313

QALY Quality-adjusted life year, *ICER* Incremental cost-effectiveness ratio, measured in cost per QALY gained, relative to letrozole

All costs and QALYs are discounted at a 3% annual rate

the first month of treatment. Such pricing schemes may serve as viable strategies for expensive but life-saving oncologic drugs, including CDK4/6 inhibitors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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