

Dear Editor,

Thank you and the respected reviewers for your precious input in reviewing our paper and providing valuable comments. Your valuable and insightful comments led to possible improvements in the current version. We have carefully considered the comments and tried our best to address each of them. We hope the manuscript after careful revisions meet your high standards. The authors welcome further constructive comments if any.

Below we provide the point-by-point responses in blue. All modifications in the manuscript have been highlighted in red.

Sincerely,

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## **Response to Reviewer #1 Comments:**

Language: The paper is well-written and understandable. I have no major concerns about the English style.

Thank you so much. We appreciate your thoughts.

There is a disproportion between introduction and discussion. In my opinion, the introduction should be shortened as some information is repeated in the discussion- mostly in the second paragraph of the introduction. Its sufficient to leave this data in the discussion, in the introduction only short information will be efficient.

Thank you so much. We have omitted some of the data mentioned in paragraph 2 related to the study settings and detailed conclusions of each study and deferred them to the discussion as suggested. Please let us know if you think we need to provide further modifications.

In the introduction, the actual place of CDK4/6 inhibitors in breast cancer treatment is not precisely specified. Provide information about visceral crisis / use of chemo vs. CDK4 / 6 inhibitors, etc.

Thank you so much. To address your comment, we have added more information in lines 45 to 50, highlighted in red. We hope this answers your concern.

Please add in the conclusion section some indications for clinicians that are the result of your study.

Thank you so much. We appreciate your thoughts. We have already included this in the current version and re-highlighted it for your kind consideration, as you can see in red in lines 419 – 420.

In line 99 please explain what the Gulf countries are as it is not obvious for everybody

Thank you so much for your comment. We have included an explanation for the Gulf countries in lines 100 and 102, as highlighted in red.

In the tables, please avoid abbreviations or explain all of them below the tables.

Thank you so much. We appreciate your comment. To address it, we have visited each of the tables and explained each of the abbreviations under the tables, as highlighted in red. We hope this answers your concern.

Conclusions: In my opinion, the article deserves publication.

Thank you so much for your time and efforts in reviewing our manuscripts. We appreciate your thoughts and valuable input and hope it meets your expectations now after the implemented modifications!

## **Response to Reviewer #2 Comments:**

The economic evaluation is interesting and appears competently performed. However, I do have some concerns, mainly about the presentation.

Thank you so much. We appreciate your thoughts. We will try our best to address your concerns as below.

The title sets out the comparison of palbociclib to ribociclib. However, the wording in the text is not as clear in terms of the comparison as in the title. See for example the aim where it is not obvious to the reader what the intervention and the alternative is.

Thank you so much for your comment. To address it, we have reworded the aim for more clarity, as you can see in line 105 onwards (highlighted in red in the manuscript).

A negative ICER cannot be interpreted and should not be calculated. I suggest that the authors either settles for presenting the incremental cost and benefits and concluding that ribociclib dominates Palbociclib, or uses the “net benefit” approach instead of the ICER.

Thank you so much. We really appreciate your comment. Therefore, we will still present ICERs with “dominant” and “dominated” terms. You will find it adjusted all over the text and highlighted in red.

P2, lines 81-83: The authors state that the results in prior research varies over settings and perspectives. Then the authors should state the perspectives of the prior.

Thank you so much for your comment. We have already stated the detailed perspectives of the existing studies while discussing them since it was more relevant to be mentioned there. We have highlighted them in red for reference on lines: 342, 347, and 352.

I think the model could use a bit more explanation to help readers that are not experts on breast cancer. For example, why is there no path to cured/healthy, what does “progression free disease” actually mean, where does the costs occur (in 1, 2 or both 1 and 2), why is the costs so much lower for PD and why is there no difference between the drugs (this is mentioned later in the article), what is the effectiveness outcome? Etc.

Thank you so much. We really appreciate your thoughts and, accordingly, have added more details to our model explanation section to make it informative, as you can see highlighted in red in lines 123 – 129 regarding the definition of each health state, line 133 regarding why there is no path for healthy/cured, and lines 112 – 113 representing the effectiveness outcomes. Regarding the no. of differences PD between drugs, this is because of the fact that a patient is managed according to progression type once a progression is developed, not according to the type of CDK4/6 inhibitor she received. This is elaborated more in the text in lines 191 to 194 (marked in red).

Table 2 includes information both relevant to the method and the results. If anything, it should be in the result section (currently method section), but be sure to explain in the method section how you vary the parameters in the sensitivity analyses (both deterministic

and probabilistic) – this is currently not done.

Thank you so much. We really appreciate your comments. Regarding table 2, we have removed the last column that included the results and replaced it with a column that includes the source of boundaries in the sensitivity analysis (highlighted in red). We have added table 5 instead to explain the results (highlighted in red starting from line 70). Regarding the variation of parameters, we have added further elaboration in the sensitivity analysis section, as highlighted in red (lines 205 – 207 for the deterministic SA, and lines 213 – 216 for PSA). We hope this answers your concern.

The text on page 6 (between tables 2 and 3) is hard to follow and should be rewritten for clarity. Also, the last sentence precedes the results.

Thank you so much. We really appreciate your thoughts. To clarify it, we have reworded it. Please check it again in lines 212 – 219 and let us know if we need further modifications for better quality.

In the first paragraph in the result section, the authors calculate the average cost-effectiveness ratio (cost/QALY) and compare this to the threshold. However, this is actually a comparison to a zero cost/zero effect alternative (i.e., immediate death), which is not a relevant alternative and therefore an inappropriate comparison. This should be excluded.

Thank you so much. Actually, upon reviewing your comment, we have removed this comparison as it is misleading, and it is the ICER that should be compared to the WTP threshold. Thank you for drawing our attention to this.

Figure 2: I see no point to this graph, and it can be removed. In addition, it is inappropriately scaled in a way to exaggerate the difference between the drugs.

Thank you so much. We really appreciate your thoughts, and we have removed it upon revision.

P8, this is better presented in a table (Table 2) – but with “dominating” instead of negative ICER (if that indeed is the interpretation).

Thank you so much. Done, and table 5 was added accordingly.

NB: Now page 9 after implementing the edits of reviewers #1 and #2.

I think the tornado diagram using net monetary benefit is a much better choice than ICER (you should consider excluding figure 3). But I don't understand who the NMB is calculated. Given that the highest CIER I can see is 198k and with a threshold value of 576k, I cannot see how you could have gotten negative NMB. ( $NMB = (\text{incremental benefit} * \text{threshold value}) - \text{incremental cost}$ ). Presumably, you have turned it around, but then it is unclear why at least one scenario give a positive NMB – but I guess it is possible the incremental costs could be high enough to give this result, but please clarify.

Thank you so much. We really appreciate your comment and understand where the concern comes from. However, regarding the calculations of NMB, we did not do it as it was not one of the objectives of this analysis. We just thought it would be good to have it represented in the Tornado diagram to give more clarification which is an automatic option provided by TreeAge Pro® using the same model inputs. We assume that one of the scenarios at least gave a negative outcome depending on the variation cost, as you assumed. But we cannot

elaborate too much on this point because it might be outside the research scope. So we are still willing to keep the tornado diagram represented in figure 3 previously (figure 2 now). Alternatively, if you think the presence of NMB in this manuscript may be a source of confusion, we can omit figure 3 (figure 4 previously) if you think it would be more appropriate.

As Figure 6 is based on Figure 5 (as I understand it), Figure 5 can be excluded. In Fig 6, I don't understand the WTP line. Shouldn't this be the threshold line, i.e., what society is willing to pay per QALY. If so, it should go through the coordinates for 576k and 12 months, but it doesn't. So what is it and how it is related to conclusion about cost-effectiveness? Potentially related to this (unclear) is the colour coding in Fig 6. What does it mean? Is it scenarios where one drug is considered to be preferable to the other? If so, it appears it is based on the wrong threshold.

Thank you so much. We really appreciate your concern. As for figure 5, we agree with your recommendation and have excluded it accordingly. Regarding figure 6 (now 4 after excluding 2 figures based on your valuable review), as we elaborated in the caption, green dots represent ribociclib, and red dots represent palbociclib. The aim of this figure is to illustrate the scenario distribution in terms of costs (Y-axis) and effectiveness (X-axis). The WTP threshold line is to give more illustration, but it is not the major thing. As you can see, the figure is divided into 4 quarters, and the scenarios are explained in terms of these 4 quarters. This was also explained in the text but re-highlighted again in red for your consideration; Lines 306 to 310.

Last sentence in the abstract states that “ribociclib is considered more cost-effective compared to palbociclib”. Since the comparison is explicit, the “more” here would refer to a comparison to another cost-effectiveness ratio. And since there is no other comparison being made, it is correct in this article to drop the “more” from the sentence. The same issue reappears in several places in the article (more/less) and should be changed accordingly.

Thank you so much for your comment. Upon reviewing it, we found it valid and we have revisited the manuscript and dropped these words, and reworded it for clarity.

P. 2, lines 58-60: Incomplete sentence.

Thank you so much! Done.

P2, lines 62-63: “existing” not “existed”. Also at the end of the page.

Thank you so much! Done.

Regarding all graphs: there is no need to have decimals on the costs, it should be stated in the graphs what the effectiveness is (not just “effectiveness”), the variables names should be readable and meaningful (see 3 and 4).

Thank you so much for your comment. Regarding the decimals, unfortunately, we could not change them since it is an original graph generated by TreeAge Pro® and this is how they format it. Regarding the variables, we agree with your point. Still, since it is a graph and only limited characters are allowed by variable, we have added an explanation downside to the

graphs regarding each of the variables' abbreviations for clarity – highlighted in red in lines 276 – 285 and lines 290 to 299.

It's base-case, not case-base.

Thank you so much! Done; changed all over the text.

P12, lines 347-348: “we relied [...] to rely”

Thank you so much for drawing our attention. Reworded to “we used a predesigned source of data to rely on for our economic analysis...” as can be seen in the highlighted lines 372 (lines numbering changed after making the previous changes).



Article

# Cost-Effectiveness and Cost-Utility of Palbociclib Versus Ribociclib in Stage IV Breast-Cancer Females: A real-world-data-based evaluation

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**Citation:** Al-Ziftawi, N.H.; Alam, M.F.; Elazzazy, S.; Shafie, A.A.; Hamad, A.; Ibrahim, M.I.M. Cost-Effectiveness and Cost-Utility of Palbociclib Versus Ribociclib in Stage IV Breast-Cancer Females: A real-world-data-based evaluation. *Int. J. Environ. Res. Public Health* **2022**, *19*, x. <https://doi.org/10.3390/xxxxx>

Academic Editor(s):

Received: date

Accepted: date

Published: date

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**Abstract:** Palbociclib and ribociclib are indicated in the first-line treatment of hormonal-receptor-positive HER-2 negative (HR+/HER-2 negative) advanced breast cancer. Despite their clinical benefit, they can increase healthcare expenditure. Yet, there are no comparative pharmacoeconomic evaluations for them in developing countries, the Middle East, or Gulf countries. This study compared the cost-effectiveness of palbociclib and ribociclib in Qatar. A 10-year within-cycle corrected Markov's model was developed using TreeAge Pro® software. The model consisted of three main health states: progression-free (PFS), progressed-disease (PD), and death. Costs were obtained from the actual hospital settings, transition probabilities were calculated from individual-patient data, and utilities were summarized from the published literature. Incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR) were compared to three gross-domestic-products per capita. Deterministic and probabilistic sensitivity analyses were performed. Ribociclib **dominated palbociclib in terms of costs, life-years gained, and quality-adjusted life-years gained**. The conclusions remained robust in the different cases of the deterministic sensitivity analyses. Taking all combined uncertainties into account, the confidence in the base-case conclusion was approximately 60%. Therefore, in HR+/HER-2 negative stage IV breast cancer patients, the use of ribociclib is considered cost-saving compared to palbociclib.

**Keywords:** Cyclin-dependent-kinase 4/6 inhibitors; advanced breast cancer; cost-effectiveness; cost-utility; cost-saving

## 1. Introduction

Breast Cancer is one of the most common non-communicable diseases worldwide ranking second amongst all cancers with a total estimated number of 627,000 deaths (6.2% of the total cancer-related deaths and 15% in women's cancer-related deaths) in 2018 [1,2]. Stage IV breast cancer, including advanced breast cancer (ABC) and metastatic breast cancer (MBC), is challenging due to being incurable with low survival rates [3]. The majority of stage IV patients are observed to be hormone receptor-positive (HR+)/human epider-

mal receptor 2-negative (HER2-) [4]. For these patients, there are several first-line treatments depending on the patient's case. Generally, endocrine therapy was considered the mainstay first-line treatment for the majority of patients with HR+ advanced breast cancer. Chemotherapy can be also used as a first-line treatment for patients who have a life-threatening disease or requires early relief of symptoms due to significant visceral organ involvement endocrine [5]. Nonetheless, cyclin-dependent kinase 4 and 6 enzymes inhibitors (CDK4/6 inhibitors) are relatively new class of medications, which were approved in the first-line treatment alongside the endocrine therapy for HR+/HER-2 negative stage IV breast cancer patients after proving their clinical superiority compared to endocrine monotherapy [5]. To date, there are three CDK4/6 inhibiting agents approved by the Food and Drug Administration (FDA): palbociclib, ribociclib, and abemaciclib [6]. CDK4/6 inhibitors are expensive, and they need frequent close monitoring due to their side effects, which include blood-related side effects (such as neutropenia, febrile neutropenia, thrombocytopenia, anemia, and leukopenia), heart-related side effects (such as affecting the QT interval and induced abnormalities in electrocardiography), gastric side effects (such as diarrhea and constipation), and generalized fatigue and neurological pain [7,8]. Therefore, although CDK4/6 inhibitors were proven to add clinical benefit as per the available randomized controlled trials and observational studies [9–16], they can increase healthcare expenditure and healthcare costs. Thus, their use should be guided by reliable pharmacoeconomic evidence.

As for the pharmacoeconomic evidence, on one hand, to date, there are a few existing comparative cost-effectiveness studies for the cost-effectiveness of palbociclib and ribociclib in stage IV HR+/HER2-negative breast cancer patients [17–21]. All of them concluded that the treatment with ribociclib plus letrozole was cost-effective compared to palbociclib plus letrozole, except for one study that concluded that both palbociclib plus letrozole and ribociclib plus letrozole combinations are not cost-effective compared to letrozole monotherapy [19]. Of note, all of these evaluations have included only a single combination with the treatment of interest, palbociclib plus letrozole versus ribociclib plus letrozole, without taking any of the other FDA-indicated combinations into consideration such as fulvestrant or tamoxifen. In addition, these analyses were based on secondary data obtained from the phase III clinical trials which were mainly the MONALEESA-2 [9], PALOMA-1 [16], and PALOMA-2 [12]. On the other hand, a recent 3-year cost-minimization analysis from Russia using more real-world data has concluded that palbociclib is a cost-saving option compared to ribociclib assuming equal clinical benefit [22]. Currently, only one comparative cost-effectiveness analysis compared the three CDK4/6 inhibiting agents in combination with fulvestrant in the USA [23]. It concluded that abemaciclib was a cost-effective option than ribociclib, but less cost-effective than palbociclib [23]. Therefore, it can be concluded that the conclusion regarding the cost-effectiveness of CDK4/6 inhibitors varies depending on the different settings and perspectives from which the pharmacoeconomic analysis is carried out.

Qatar is an Arab country with a diverse population, where more than 80% of the population is not Qatari and comes from different ethnicities [24]. In Qatar, breast cancer remains challenging being the first common type of cancer accounting for 31% of the total new cases of cancer in 2018 [25]. The healthcare system in Qatar is a nonprofit healthcare system in which it is the main payer for healthcare services to all citizens and residents [26]. Cancer care is mainly provided by the National Center for Cancer Care and Research (NCCCR), which is the premier hospital for managing cancer in the state of Qatar and one of the main hospitals under Hamad Medical Corporation [27]. For stage IV HR+/HER-2 negative breast cancer patients, CDK4/6 inhibitors are used in the treatment of these patients; however, it is only palbociclib and ribociclib that are authorized in the formulary so far. Due to the nature of the healthcare system in Qatar where the government pays 100% of the cancer care on behalf of patients, and due to the fact that CDK4/6 inhibitors can increase healthcare costs, it is important to have strong cost-effectiveness evidence to

guide their optimal use. To date, there are no cost-effectiveness analyses comparing palbociclib and ribociclib conducted in Qatar, nor in countries with similar healthcare systems and economic situations to Qatar such as the Gulf countries —the regional, intergovernmental, political, and economic countries union comprising Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates, or the Middle East. The existing cost-effectiveness analyses conducted worldwide may be misleading to be adopted to Qatar due to the different perspectives, populations, and economic profiles. Therefore, this study aims to compare the cost-effectiveness of palbociclib and ribociclib with their all approved FDA combinations in stage IV HR+/HER-2 negative breast cancer females in the state of Qatar, which can also serve as a guide for countries with similar healthcare and economic profiles to Qatar.

## 2. Materials and Methods

### 2.1. Overview

A 10-year within-cycle-corrected Markov decision analytical model was developed to estimate the overall costs, and effectiveness represented in life years gained, and quality-adjusted life years gained for the targeted population. The model was carried out from the healthcare payer perspective, Hamad Medical Corporation- NCCCR. The incremental cost-effectiveness ratio (ICER) was compared to a willingness-to-pay (WTP) threshold of fewer than three times the national annual gross domestic product (GDP) per capita as per the World Health Organization (WHO) for cost-effective interventions [28]. As a result, a treatment regimen of an incremental cost of less than 576,150 QAR per QALY gained is considered to be cost-effective and very cost-effective if it is less than 192,050 QAR per QALY, based on the Qatari GDP/ capita of 52,751 USD (1 USD = 3.65 QAR, 2020 financial year) [29]. All costs and outcomes were discounted by an annual discounting rate of 3.5%.

The model was composed of three health states: ‘progression-free disease’ which is defined in this model as the length of time in months that a patient can live with breast cancer while receiving palbociclib or ribociclib but without dying from tumor progression or following adverse events of the treatment, ‘progressed disease’ which is the length of time a patient can live with breast cancer after developing any increase in tumor size or new development of lymphadenopathy or distant metastasis, and ‘death’ which is the absorbing state in this model. All patients were assumed to enter the model in the ‘progression-free disease’ state. The transition between the health states follows a unidirectional transition way, where at the end of each cycle, a patient can stay in the same state or move to the next state or move directly to death, with no back transition to the previous state; this is due to the disease nature since stage IV breast cancer is not curable. The Markov cycle length is assumed to be one month since it is the normal evaluation for the event development as per the clinical guidelines. A visualization of Markov’s model for this study is illustrated in Figure 1. The model was developed and analyzed using the TreeAge Pro 2020 ® software.

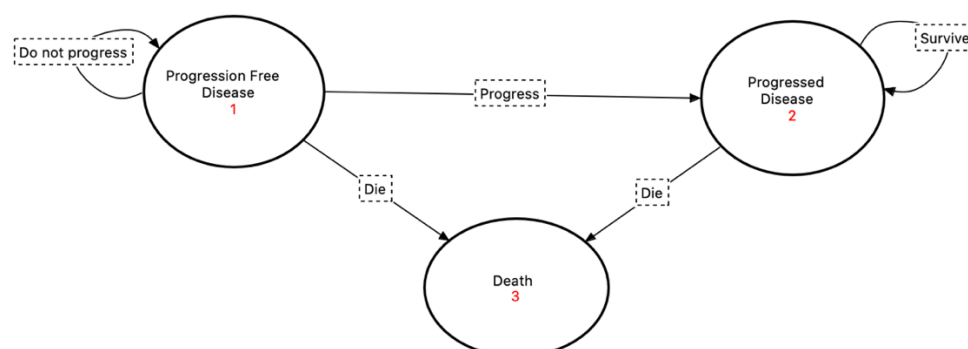


**Figure 1.** Visualization of the Markov's model implemented in the study with the state diagram and their transitions' pathways.

## 2.2. Model Inputs

The model inputs included costs, transition probabilities between health states, and effectiveness parameters (life months and utilities). These were estimated based on individual patients' data and based on published literature to feed the model as follows:

- Costs

The total direct medical costs per patient per month for each health state in each treatment strategy were calculated based on individual patients' data inputs. The unit costs were obtained from the department of accounting and finance in Hamad Medical Corporation based on the 2019/2020 financial year. All costs were calculated in the local currency, Qatar riyals (1 USD = 3.65 QARs). For each of the two comparators, palbociclib, and ribociclib, all cost components were analyzed based on the following components: drug acquisition cost, combination drug acquisition cost, laboratory tests needed throughout the treatment period [complete blood count (CBC), blood chemistry tests (comprehensive metabolic panel, liver function test, magnesium and phosphorus levels), endocrinology tests (25-hydroxyvitamin D, TSH receptor antibody, Follicle stimulating hormone, vitamin B12), tumor markers and catechol amines (thyroglobulin, and carcinoembryonic antigen, CEA), coagulation tests, and urine analysis test, clinical radiology costs [X-ray, ultrasound, mammogram, magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography scan (PET scan), and the bone density DEXA scan], required cardiac procedure for the CDK4/6 inhibitors costs [electrocardiogram (ECG), and echocardiogram], costs of the outpatient visits and hospitalization costs.

- Effectiveness-based transition probabilities

The monthly transition probabilities were calculated from the real evidence of individual patient data based on HR+/HER2- stage IV breast cancer patients who take, or were taking, palbociclib or ribociclib from January 2016 to January 2020 at the NCCCR in Qatar. Firstly, cumulative probabilities of each of the events of interest for the two comparators were calculated based on **Equation 1**, where  $P$  is the probability and  $A$  is the event of interest. Secondly, the cumulative probabilities were converted into a rate as per the below **Equation 2**, where  $p$  is the cumulative probability,  $r$  is the rate, and  $t$  is the time in years [30]. Lastly, the rate was converted back to 1-month transition probability as per **Equation 3** [30]. Therefore, three unique transition probabilities with two complementary ones for each arm were generated as follows: monthly transition probability from PFS to PD, monthly transition probability from PFS to death, their complementary probability of staying in the PFS, monthly transition probability from PD to death, and its complementary monthly probability of staying PFs for both groups. All the transition probabilities, utility values [31–33] and discounting rate [34] are summarized in **Table 1**.

$$P(A) = \frac{\text{Total number of cohort with event (A)}}{\text{Total number of cohort}}$$

**Equation 1.** Cumulative probability of event (A) for a patient cohort

$$r = -\frac{\ln(1 - P)}{t}$$

**Equation 2.** Constant rate from probability

$$\text{Time probability (A)} = 1 - \exp(-r \cdot t)$$

**Equation 3.** Fixed time probability

- Utilities

Quality of life was used to investigate the impact of the quality of life (QoL) on every additional year gained by the treatment of palbociclib and ribociclib to generate quality-

adjusted life years (QALYs). QoL values were obtained from the published literature [31–33]. QoL values for the ‘progression-free disease’ health state were summarized from published literature from findings from the PALOMA-2 trial for the palbociclib group [31], and from the MONALEESA-3 trial for the ribociclib group [32]. For the ‘progressed disease’ health state, it was assumed that there was no difference in terms of the quality of life between palbociclib and ribociclib. **This assumption is based on the fact that when a patient develops a progression, she is managed according to the same hospital guidelines depending on the progression type she had and regardless of the CDK4/6 inhibiting drug that she received before.** Therefore, the same utility value of 0.45 was used as per a published literature systematic review [33]. All utility values, and other model inputs, are summarized in **Table 1**.

**Table 1.** Inputs of the Markov's model.

| Model Input                      | Value     | Minimum | Maximum  | SD    | Source of Data |
|----------------------------------|-----------|---------|----------|-------|----------------|
| Costs/ Months (QAR)              |           |         |          |       |                |
| PFS (Palbociclib)                | 11,628.5  | 7,477.4 | 14,316.4 | -     | RWD            |
| PFS (Ribociclib)                 | 10,258.1  | 8926.4  | 11,054.2 | -     | RWD            |
| PD                               | 2,942.6   | 1,893.9 | 4,118.3  | -     | RWD            |
| Utility Values                   |           |         |          |       |                |
| PFS (Palbociclib)                | 0.7507    | 0.7387  | 0.7627   | -     | [31]           |
| PFS (Ribociclib)                 | 0.710     | -       | -        | 0.185 | [32]           |
| PD                               | 0.45      | -       | -        | -     | [33]           |
| Monthly Transition Probabilities |           |         |          |       |                |
| PFS to PD (Palbociclib)          | 0.0459708 | -       | -        | -     | RWD            |
| PFS to death (Palbociclib)       | 0.0005916 | -       | -        | -     | RWD            |
| PD to death (Palbociclib)        | 0.0116347 | -       | -        | -     | RWD            |
| PFS to PD (Ribociclib)           | 0.0588690 | -       | -        | -     | RWD            |
| PFS to death (Ribociclib)        | 0.0029835 | -       | -        | -     | RWD            |
| PD to death (Ribociclib)         | 0.0063706 | -       | -        | -     | RWD            |
| Discounting Rate                 |           |         |          |       |                |
|                                  | 3.5%      | 1.5%    | 3.5%     | -     | [34]           |

PFS: Progression-free survival

PD: Progressed disease

RWD: Real-World data

### 2.3. Sensitivity Analysis

To address the impact of any uncertainties regarding the model inputs on the conclusion of the cost-effectiveness or cost-utility, a univariate deterministic sensitivity analysis was implemented with a single scenario with each variable assessment. The variables assessed through the deterministic sensitivity analysis were: costs, transition probabilities from 'progression-free disease' to 'progressed disease', and quality of life for each health state. In order to ensure the robustness of the output, each of the variables of interest was varied separately while fixing the other model inputs and ICER and ICUR were calculated accordingly. Then, a tornado analysis was generated to determine the variables who has the maximum effect on the cost-effectiveness conclusion. Deterministic sensitivity analysis inputs and source of the inputs' boundaries are summarized in Table 2.

**Table 2.** Univariate sensitivity analysis inputs.

| Input Parameter                                  | Base-case Value | Sensitivity analysis boundaries |                | Source of Data           |
|--------------------------------------------------|-----------------|---------------------------------|----------------|--------------------------|
|                                                  |                 | Lower boundary                  | Upper boundary |                          |
| Cost of PFS State for Palbociclib (QAR)          | 11,628.5        | 9,302.8                         | 13,954.2       | ± 20% of base-case value |
| Cost of PFS State for Ribociclib (QAR)           | 10,285.1        | 8,228.1                         | 12,342.1       | ± 20% of base-case value |
| Cost of Progressed Disease state (QAR)           | 2,942.6         | 2,354.1                         | 3,531.1        | ± 20% of base-case value |
| Monthly Probability for PFS to PD in Palbociclib | 0.04597         | 0.04597                         | 0.05036        | [12, 13]                 |
| Monthly Probability for PFS to PD in Ribociclib  | 0.05887         | 0.0261                          | 0.05887        | [9]                      |
| Utility of PFS State for Palbociclib             | 0.7507          | 0.738                           | 0.7627         | [31]                     |
| Utility of PFS state for Ribociclib              | 0.7             | 0.5705                          | 0.8295         | [32]                     |
| Utility of PD State                              | 0.45            | 0.36                            | 0.54           | [33]                     |

Additionally, a probabilistic sensitivity analysis (PSA) was implemented using Monte-Carlo simulation analysis based on unique 10,000 simulations. Therein, the parameters are input as distributions rather than just fixed values and the different distributions of the different parameters are varied together to generate 10,000 different scenarios with possible outcomes. The detailed inputs of the Monte-Carlo analysis are summarized in **Table 3**. In addition, the incremental cost-effectiveness plot (ICE) was generated to illustrate the ratio of the simulations favoring ribociclib treatment versus palbociclib treatment, and the overall confidence of the base-case conclusion was generated.

**Table 3.** Probabilistic sensitivity analysis inputs.

| Input                                            | Distribution | Point Estimate | Standard Deviation |
|--------------------------------------------------|--------------|----------------|--------------------|
| Cost of PFS State for Palbociclib (QAR)          | Gamma        | 11,628.515     | 6,838.95           |
| Cost of PFS State for Ribociclib (QAR)           | Gamma        | 10,285.092     | 2,127.73           |
| Cost of PD state (QAR)                           | Gamma        | 2,942.6        | 2,224.34           |
| Monthly Probability for PFS to PD in Palbociclib | Beta         | 0.04597        | 0.01364            |
| Monthly Probability for PFS to PD in Ribociclib  | Beta         | 0.05887        | 0.0260             |
| Utility of PFS State for Palbociclib             | Beta         | 0.75           | 0.1290             |
| Utility of PFS state for Ribociclib              | Beta         | 0.70           | 0.185              |
| Utility of PD State                              | Beta         | 0.45           | 0.20               |

PFS: Progression-free survival

PD: Progressed disease

QAR: Qatari Riyal

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### 3. Results

As per Markov's model, the 10-year cost of the palbociclib treatment strategy was 372,663.3 QAR. In accordance, it has yielded a gain of 5.968 life years (LYs) and overall gained quality-adjusted life years (QALYs) of 3.058. Whereas, for the ribociclib treatment arm, the estimated 10-year cost was 333,584.4 QAR. Similarly, it has yielded 6.330 gained life years and 3.160 QALYs. The costs and effectiveness values were incremented to compare the two treatment options. Ribociclib **was dominant over** palbociclib at a 3-GDP and 1-GDP thresholds. The detailed values of the base-case overall cost and effectiveness are shown in **Table 4**.

**Table 4.** Base-case results for palbociclib and ribociclib treatment groups.

|                               | Palbociclib | Ribociclib | Palbociclib minus Ribociclib |
|-------------------------------|-------------|------------|------------------------------|
| <b>Cost (QAR)</b>             |             |            |                              |
| Total Cost                    | 372,663.3   | 333,584.4  | 39,078.9                     |
| PFS Cost                      | 229,563.45  | 154,170.39 | 75,393.06                    |
| PD Cost                       | 143,099.89  | 179,414.02 | – 36,314.13                  |
| <b>Effectiveness Outcomes</b> |             |            |                              |
| Life Years Gained             | 5.968       | 6.330      | – 0.362                      |
| QALYs Gained                  | 3.058       | 3.160      | – 0.102                      |
| <b>Incremental Ratios</b>     |             |            |                              |
| ICER                          | -           | -          | <b>Dominated</b>             |
| ICUR                          | -           | -          | <b>Dominated</b>             |

QAR: Qatari Riyal

PFS: Progression-free survival

PD: Progressed disease

ICER: Incremental cost-effectiveness ratio

ICUR: Incremental cost-utility ratio

Regarding the univariate deterministic sensitivity analysis, the base-case conclusion of having ribociclib as a cost-effective option remained robust against the variation of the cost of PFS for the palbociclib group. However, it was shown that palbociclib was not dominated as described previously at a cost of PFS that equals 9,612.9 QAR (17.33% reduction of the input cost); however, it was still **not cost-effective compared** to ribociclib in total (ICUR = 5572.79 QAR/ QALY gained per patient). Similarly, in absence of any other uncertainties, the conclusion of the cost-effectiveness and cost-utility of the two medications remained the same keeping ribociclib **dominant** over palbociclib with +/- 20% adjustment in the total cost of PFS cost of ribociclib; ICUR ranged from -6,723.5 QAR/QALY to -57,012.6 QAR/QALY. As for the transition probabilities of PFS to PD in the palbociclib arm, when applying the uncertainty range of (0.0459 – 0.05035), the conclusion of having ribociclib **dominant** over palbociclib remained robust against this uncertainty variation in absence of any other uncertainties. On the other hand, for the monthly probability of PFS to PD for the ribociclib group, ribociclib remained cost-effective than palbociclib when the probability was varied according to the MONALEESA-2 trial; nonetheless, it was dominant only when the probability is more than or equals 0.04537 (25% variation from the base-case probability). The uncertainty regarding the probability of PFS to PD in the ribociclib treatment arm was associated with an ICUR ranging from 12,894.35 QAR/QALY to

-31,868.06 QAR/QALY suggesting ribociclib is either a cost-effective option or a dominant option. Lastly, the utility associated with the PFS of palbociclib was varied according to the 95% CI range of the base-case (0.7387 – 0.7627). The conclusion of the cost-effectiveness of ribociclib over palbociclib remained robust over that range of uncertainty where ribociclib was dominant over palbociclib over all the uncertainty range; ICUR ( -26,458.52 QAR/QALY to -39,498.59 QAR/QALY). Similarly, the conclusion of the cost-effectiveness of ribociclib over palbociclib remained robust when the utility of PFS in the ribociclib group was varied by 18.5% according to the standard deviation associated with the utility value as obtained from the literature. That is, ribociclib was cost-effective than palbociclib all over the uncertainty range, however, it did not dominate palbociclib at utility values less than 0.622; ICUR ranged from 54,664.07 QAR/QALY to 198,120.36 QAR/QALY. Lastly, the utility of progressed disease varied at +/- 20%, and the conclusion of the domination of ribociclib over palbociclib remained robust all over the range; ICER ranged from -338,058.56 QAR/QALY to -16,722.21 QAR/QALY. A tornado diagram was generated to illustrate the effect of the individual factors' uncertainty on the overall cost-effectiveness conclusion; **Figure 2**. In addition, although the net monetary benefit was not of the outcomes of this research, the tornado diagram was plotted against the net monetary benefit for more clarification and illustration. The results are consistent with what was drawn by the tornado diagram on ICER as can be illustrated in below **Figure 3**. All the sensitivity analysis inputs and outputs are illustrated in **Table 5**.

**Table 5.** Univariate sensitivity analysis inputs and outputs.

| Sensitivity Analysis Parameter                   | Sensitivity analysis boundaries |                | ICER range (QAR/QALY) |                |
|--------------------------------------------------|---------------------------------|----------------|-----------------------|----------------|
|                                                  | Lower boundary                  | Upper boundary | Lower boundary        | Upper boundary |
| Cost of PFS State for Palbociclib (QAR)          | 9,302.8                         | 13,954.2       | Dominant              | 5,572.8        |
| Cost of PFS State for Ribociclib (QAR)           | 8,228.1                         | 12,342.1       | Dominant              | Dominant       |
| Cost of Progressed Disease state (QAR)           | 2,354.1                         | 3,531.1        | Dominant              | Dominant       |
| Monthly Probability for PFS to PD in Palbociclib | 0.04597                         | 0.05036        | Dominant              | Dominant       |
| Monthly Probability for PFS to PD in Ribociclib  | 0.0261                          | 0.05887        | Dominant              | 12,894.4       |
| Utility of PFS State for Palbociclib             | 0.738                           | 0.7627         | Dominant              | Dominant       |
| Utility of PFS state for Ribociclib              | 0.5705                          | 0.8295         | Dominant              | 198,120.3      |
| Utility of PD State                              | 0.36                            | 0.54           | Dominant              | Dominant       |

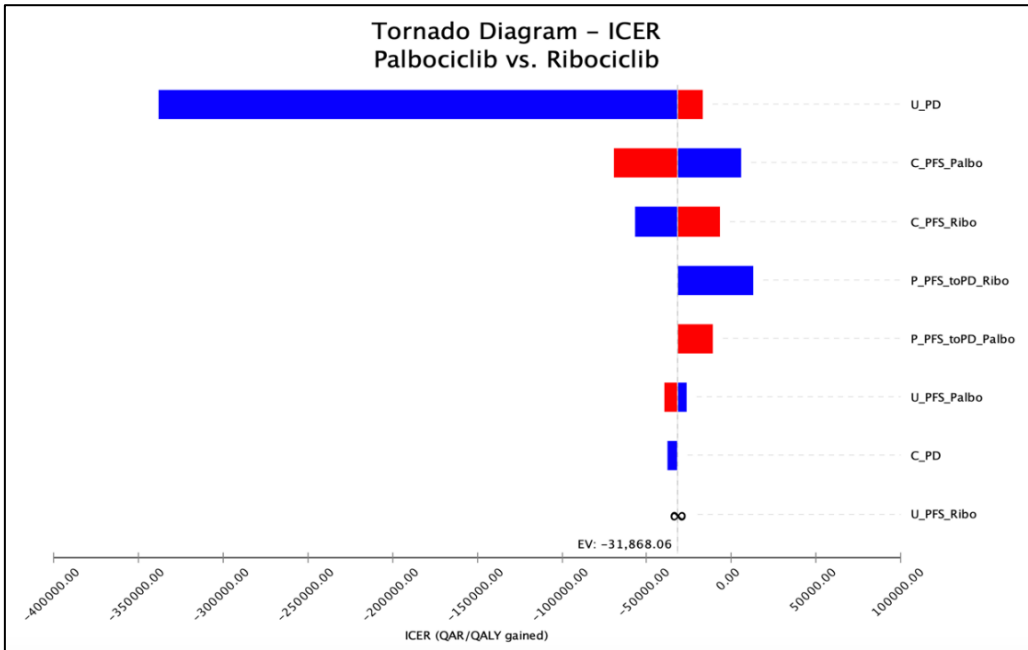


**Figure 2.** Tornado diagram of the univariate sensitivity analyses and their Impact on ICER. The blue color represents the parameter, whereas the red color represents the ICER. ICERs are ICURs (QAR/QALY).  
U\_PD: the utility value of the ‘progressed disease’ health state  
C\_PFS\_Palbo: the cost of the ‘progression-free survival’ health state for ‘palbociclib’ treatment group  
C\_PFS\_Ribo: the cost of the ‘progression-free survival’ health state for ‘ribociclib’ treatment group  
P\_PFS\_toPD\_Ribo: the transition probability from the ‘progression-free survival’ health state to the ‘progressed disease’ health state for ‘ribociclib’ treatment group  
P\_PFS\_toPD\_Palbo: the transition probability from the ‘progression-free survival’ health state to the ‘progressed disease’ health state for ‘palbociclib’ treatment group  
U\_PFS\_Palbo: the utility value of the ‘progression-free survival’ health state for ‘palbociclib’ treatment group  
U\_PFS\_Ribo: the utility value of the ‘progression-free survival’ health state for ‘ribociclib’ treatment group  
C\_PD: the cost of the ‘progressed disease’ health state

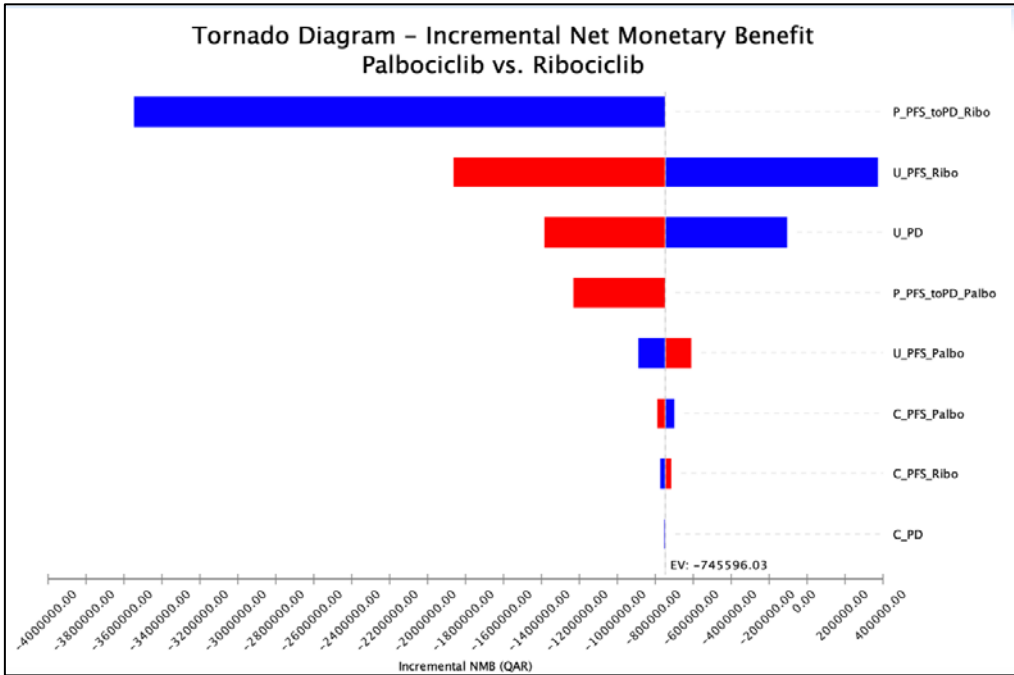


**Figure 3.** Tornado diagram of the univariate sensitivity analyses and their impact on incremental net monetary benefit (NMB). The blue color represents the parameter, whereas the red color represents the NMB. NMB is expressed in Qatari riyals.

P\_PFS\_toPD\_Ribo: the transition probability from the 'progression-free survival' health state to the 'progressed disease' health state for 'ribociclib' treatment group  
 U\_PFS\_Ribo: the utility value of the 'progression-free survival' health state for 'ribociclib' treatment group  
 U\_PD: the utility value of the 'progressed disease' health state  
 P\_PFS\_toPD\_Palbo: the transition probability from the 'progression-free survival' health state to the 'progressed disease' health state for 'palbociclib' treatment group  
 U\_PFS\_Palbo: the utility value of the 'progression-free survival' health state for 'palbociclib' treatment group  
 C\_PFS\_Palbo: the cost of the 'progression-free survival' health state for 'palbociclib' treatment group  
 C\_PFS\_Ribo: the cost of the 'progression-free survival' health state for 'ribociclib' treatment group  
 C\_PD: the cost of the 'progressed disease' health state

Lastly, as for the probabilistic sensitivity analysis by Monte-Carlo simulation, the mean (SD) lifetime cost of palbociclib was 386,778.1 (196,998.1) QAR with an average (SD) gained QALYs of 3.135 (0.8725) QALYs. For the ribociclib treatment group, the mean (SD) lifetime cost according to the generated simulations was 354,057.03 (152,369) QAR with an average (SD) gained QALYs of 3.246 (1.0425) QALYs. To graphically test the base-case conclusion of preferring ribociclib over palbociclib, the ICE plot of ribociclib versus palbociclib was generated (Figure 4). According to the figure, the major distribution of the generated scenarios showed that ribociclib was effective and less costly in 26.14%, whereas it was costlier but more effective (cost-effective) in 32.87% of the cases. Nonetheless, it was less costly but less effective than in 24.65% of the cases, and inferior to palbociclib in 15.16% of the cases.

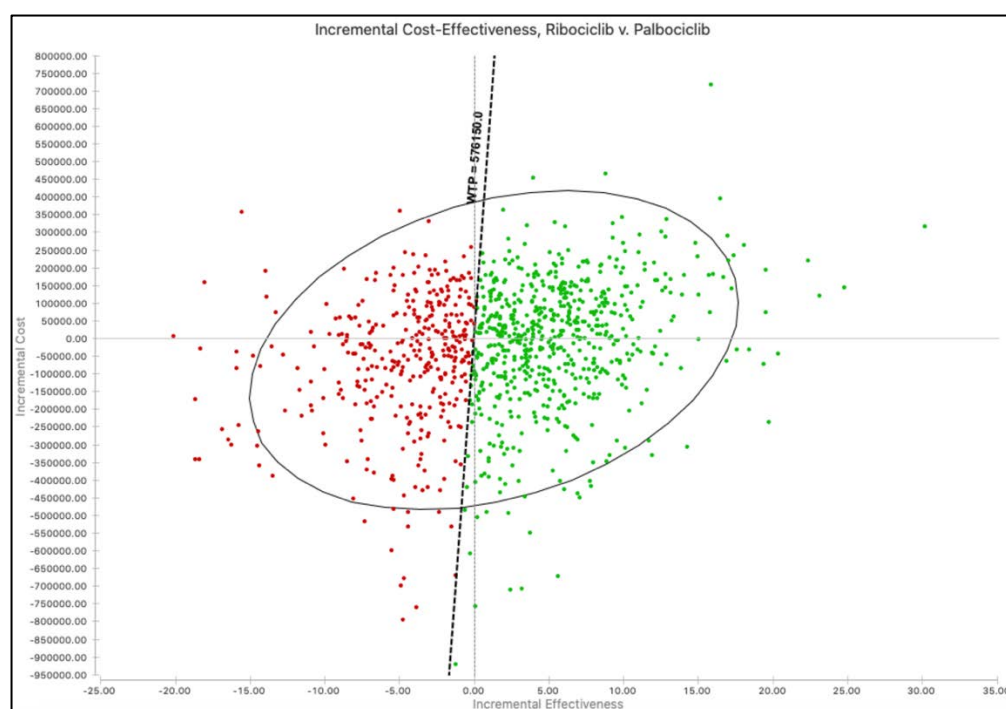


**Figure 4.** ICE plot of ribociclib versus palbociclib. Green dots are ribociclib scenarios and red dots represent the palbociclib..

#### 4. Discussion

In this research, we aim at identifying the long-term cost, the long-term effectiveness, and the incremental cost-effectiveness of two treatment strategies that are used in the first-line treatment of HR+/HER-2 negative stage IV breast cancer. Therefore, a 10-year Markov's model was run to summarize the long-term cost (QARs), effectiveness (LYs), and utility (QALYs) for each of the two treatment strategies. Overall, in our base-case analysis, the treatment with ribociclib was dominant over palbociclib in terms of both ICER and

ICUR. The finding of having ribociclib was cost-effective than palbociclib remained robust against all the one-way sensitivity analyses at the 3 GDP WTP threshold (cost-effectiveness threshold). For the 1 GDP WTP threshold (very cost-effectiveness threshold), only the uncertainty regarding one factor, the utility of PFS status in the ribociclib treatment arm, yielded an ICUR above the 1 GDP (198,120.3 QAR/QALY) suggesting that ribociclib is not a very cost-effective option. However, compared to the recommended 3 GDP WTP threshold as per the WHO, ribociclib is still a cost-saving option compared to palbociclib even with the uncertainty associated with that factor. Of note, our conclusion remained robust against the probabilistic sensitivity analysis that is associated with the combined uncertainties of all factors. Approximately 60% of the yielded hypothetical 10,000 scenarios in the Monte Carlo simulation suggested that ribociclib is cost-effective compared to palbociclib.

To date, and up to our knowledge, there are four comparative pharmacoeconomic evaluations regarding the cost-effectiveness and the cost-utility of palbociclib and ribociclib. The findings of our study were consistent with three of them. That is, in a study conducted in Spain by Galve-Clavo et. al (2018) to evaluate the ICER and ICUR of ribociclib plus letrozole versus palbociclib plus letrozole, the former was associated with an ICER of Euros 1,007.69 (QAR 4360.56) per every additional life year gained and an ICUR of Euros 1,543.62 (QAR 6,679.69) per each QALY gained, at a threshold of 30,000 Euros/QALY (129,818.59 QAR) [17]. Therefore, this study revealed that ribociclib was also cost-effective and cost-useful compared to palbociclib **from the Spanish National Health System perspective** [17]. In another study by Mistry R. et al. (2018) conducted in the USA also comparing ribociclib plus letrozole versus palbociclib plus letrozole versus letrozole monotherapy, ribociclib was dominant over palbociclib with a cost-saving of 43,037 USD, and also was still cost-effective compared to letrozole monotherapy option [18]. **That pharmacoeconomic analysis was conducted from the USA private third-party payer perspective** at a WTP threshold of 198,000 USD/QALY (720,918.06 QAR/QALY) [18]. Our findings were also consistent with one more pharmacoeconomic analysis by Suri G. et al (2019) conducted in the UK where also ribociclib plus letrozole was compared to palbociclib plus letrozole [20]. Their study reported that ribociclib plus letrozole was a cost-effective treatment strategy **from the National Health Services (NHS) and Personal Social Services (PSS) perspective in the UK** at a WTP threshold of 30,000 euro/QALY [20]. Only in one cost-effectiveness study conducted in the USA, neither palbociclib nor ribociclib were cost-effective options, and the reason for this is that the ICER was calculated for each of the two comparators versus letrozole monotherapy [19]. There was no incremental cost-effectiveness ratio between the two CDK4/6 inhibitors, and therefore, none of them was cost-effective compared to letrozole monotherapy [19].

Although the previous pharmacoeconomic analyses were all of high quality, we could not rely on their findings to generate conclusions applicable to Qatar settings for multiple reasons. First, the generalizability of pharmacoeconomic analyses across the countries is sometimes impaired due to the different sources of price weights among different countries [35], and due to different perspectives from which the pharmacoeconomic analyses take place [36]. Second, all used the published phase III clinical trials as the source for their simulated cohort, probabilities, effectiveness, and utility endpoints. Despite the success of the analysis, in the end, the use of these phase III trials itself is associated with some limitations since they were not designed basically to catch both clinical and economic endpoints. That is, in many of the pharmacoeconomic analyses based on RCTs, they try to summarize the economic outcomes from the pre-collected primary clinical outcomes, so the sources of the economic data are not primary [35]. Both the MONALEESA and the PALOMA trials from which the four pharmacoeconomic analyses took their data were not predesigned to catch economic data. Therefore, **we used a predesigned source of data to rely on for our economic analysis**, the observational study conducted by our team earlier in 2021. Third, the four pharmacoeconomic analyses all compared the use of palbociclib versus ribociclib with only one of the indicated combinations, letrozole. This

is because they used the same published phase III trial cohorts and interventions for their data. We sought a more thorough pharmacoeconomic analysis considering all the FDA-approved treatment combinations; especially since the COX regression conducted in phase I concluded no statistically significant difference in efficacy between the different treatment combinations. As a result, our analysis filled these gaps providing a powerful pharmacoeconomic analysis that can be doubtlessly used for decision-makers in Qatar and other countries with similar health economic considerations.

Our study had several strengths. To begin, it was the first pharmacoeconomic evaluation evaluating the cost-effectiveness and the cost-utility of CDK4/6 inhibitors in Qatar, the Gulf region, and the Middle East and North Africa (MENA) region in general. Therefore, the findings of our current pharmacoeconomic analysis can be used locally and regionally in countries that have similar economic profiles and healthcare systems with mild modifications to fit their context. Moreover, it is the first pharmacoeconomic analysis regarding these two treatments that were based on real-world evidence rather than just a simulation from clinical trials, avoiding all the disadvantages of modeling from clinical trials. Besides, it is the first pharmacoeconomic evaluation that compares palbociclib and ribociclib with all their FDA-indicated combinations; other analyses compared only the CDK4/6 inhibitors plus letrozole. In addition, it included pre/post-menopausal females in the cohort, unlike the other analyses that included only post-menopausal females as their cohort. Lastly, we performed an internal critical appraisal for our pharmacoeconomic study using the Quality of Health Economic Study (QHES) evaluation tool to assure the quality of the produced analysis, so we can assume that our results are assured of validity with minimal bias. However, our research had the main limitation that the **base-case** results were generated using observational real-world evidence, which itself has some limitations and potential uncertainties. However, we could address this limitation by incorporating both deterministic and probabilistic sensitivity analyses that relied on phase III published RCTs. Our pharmacoeconomic conclusions remained robust against the uncertainties in both the deterministic and the probabilistic sensitivity analyses.

Based on our study findings, we have several recommendations for the current practice and future research. First, since ribociclib had a lower overall cost than palbociclib although it has a higher acquisition cost in general, further evaluation about the consumption of the related resources needs to be conducted in the future, but with a larger sample size for both treatment arms. Second, all the published pharmacoeconomic agents included only palbociclib and ribociclib in their analyses. Abemaciclib is another CDK4/6 inhibitor that was under-addressed by pharmacoeconomic evaluations. Thus, more comparative pharmacoeconomic evaluations need to be conducted about this medication along with the other two medications in the same CDK4/6 inhibiting family.

## 5. Conclusions

Since their introduction to the market, the use of CDK4/6 inhibitors is increasing due to their proven clinical efficacy. Nonetheless, they can increase health expenditure due to their high acquisition cost and monitoring cost. Therefore, herein, we underwent a thorough cost-effectiveness analysis using a well-designed Markov model. Ribociclib was a cost-effective than palbociclib at a 3 GDP threshold and at a 1 GDP threshold suggesting **that ribociclib should be a more favorable option over palbociclib to use in practice whenever applicable**. This conclusion remained robust against the different single uncertainties as well as combined uncertainties. As a result, ribociclib was proven to be generally a cost-effective than palbociclib in the state of Qatar. This finding can be generalizable to countries having similar economic profiles, considerations, and cost drivers to Qatar. More similar pharmacoeconomic analyses that include the three CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) need to be conducted for more robust comparisons.

**Author Contributions:** All authors contributed to the work and approved the final version of the manuscript. Conceptualization, M.I. and M.A.; Methodology, N.A., M.A., and A.S.; Software, N.A.;

Validation, M.A., A.S., A.H. and M.I.; Formal Analysis, N.A.; Investigation, N.A.; Resources, M.I.,  
and M.A.; Data Curation, N.A.; Writing – Original Draft Preparation, N.A.; Writing – Review &  
Editing, M.I., M.A., S.E., A.S., and A.H.; Visualization, N.A., M.I., S.E., M.A., A.S., and A.H.; Super-  
vision, M.I., M.A., and S.E.; Project Administration, N.A.; Funding Acquisition, M.I. and S.E.

**Funding:** This study is funded by Qatar University, by financial grant #No. QUST-1- CPH- 2019-12.

**Acknowledgments:** The authors would like to acknowledge Qatar University for the funding of  
this study.

**Institutional Review Board Statement:** The study was firstly ethically approved by the Medical  
Research Center (MRC) in Hamad Medical Corporation on January 30, 2020, under the protocol  
approval number: MRC- 01-19-318, followed by the approval from the Qatar University Interna-  
tional Review Board (QU-IRB) on February 10, 2020, under the approval number: QU-IRB- 1231-  
E/20.

**Informed Consent Statement:** Not Applicable.

**Data Availability Statement:** All data generated or analyzed during this study are included in this  
article. Further enquiries can be directed to the corresponding author.

**Conflicts of Interests:** The authors deny the existence of any affiliation of personal, professional or  
financial, or any other type of conflict of interests.

## References

1. International Agency for Research on Cancer. Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018 [Internet]. World Health Organization. 2018 [cited 2021 Aug 15]. Available from: <https://www.who.int/cancer/PRGlobocanFinal.pdf?ua=1>
2. World Health Organization. Cancer Report 2020- Global Profile [Internet]. 2020 [cited 2021 Aug 15]. Available from: [https://www.paho.org/hq/index.php?option=com\\_docman&view=download&category\\_slug=4-cancer-country-profiles-2020&alias=51561-global-cancer-profile-2020&Itemid=270&lang=fr](https://www.paho.org/hq/index.php?option=com_docman&view=download&category_slug=4-cancer-country-profiles-2020&alias=51561-global-cancer-profile-2020&Itemid=270&lang=fr)
3. American Cancer Society. Survival Rates for Breast Cancer [Internet]. [cited 2021 Feb 25]. Available from: <https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-survival-rates.html>
4. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LAG, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *Journal of National Cancer Institute*. 2014 Apr 28;106(5).
5. Lurie RH, Anderson BO, Abraham J, Aft R, Agnese D, Allison KH, et al. NCCN Guidelines Version 5.2020 Breast Cancer 2020.
6. Shah M, Nunes MR, Stearns V. CDK4/6 Inhibitors: Game Changers in the Management of Hormone Receptor-Positive Advanced Breast Cancer? *Oncology (Williston Park)*. 2018;32(5):216–22.
7. Highlights of prescribing information: ibrance (palbociclib). FDA [Internet]. [cited 2021 Sep 20]. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/212436lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212436lbl.pdf)
8. Highlights of prescribing information: kisqali (ribociclib). FDA [Internet]. [cited 2021 Sep 20]. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/209092s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209092s000lbl.pdf)
9. Hortobagyi GN, Stemmer SM, Burris HA, Yap Y-S, Sonke GS, Paluch-Shimon S, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *New England Journal of Medicine*. 2016 Nov 3;375(18):1738–48.
10. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *Journal of Clinical Oncology*. 2018 Aug 20;36(24):2465–72.
11. Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncology*. 2018 Jul 1;19(7):904–15.
12. Finn RS, Martin M, Rugo HS, Jones S, Im S-A, Gelmon K, et al. Palbociclib and Letrozole in Advanced Breast Cancer. *New England Journal of Medicine*. 2016 Nov 17;375(20):1925–36.
13. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncology*. 2016 Apr 1;17(4):425–39.
14. Sledge GW, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2-advanced breast cancer who had progressed while receiving endocrine therapy. *Journal of Clinical Oncology*. 2017 Sep 1;35(25):2875–84.
15. Goetz MP, Toi M, Campone M, Trédan O, Bourayou N, Sohn J, et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. *Journal of Clinical Oncology*. 2017 Nov 10;35(32):3638–46.
16. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncology*. 2015 Jan;16(1):25–35.
17. Galve-Calvo E, González-Haba E, Gostkorszewicz J, Martínez I, Pérez-Mitru A. Cost-effectiveness analysis of ribociclib versus palbociclib in the first-line treatment of HR+/ HER2- advanced or metastatic breast cancer in Spain. *ClinicoEconomics and Outcomes Research*. 2018 Nov;10:773–90.
18. Mistry R, May JR, Suri G, Young K, Brixner D, Oderda G, et al. Cost-Effectiveness of Ribociclib plus Letrozole Versus Palbociclib plus Letrozole and Letrozole Monotherapy in the First-Line Treatment of Postmenopausal Women with HR+/HER2- Advanced or Metastatic Breast Cancer: A U.S. Payer Perspective. *Journal of Managed Care & Specialty Pharmacy*. 2018 Jun;24(6):514–23.
19. Zhang B, Long EF. Cost-effectiveness analysis of palbociclib or ribociclib in the treatment of advanced hormone receptor-positive, HER2-negative breast cancer. *Breast Cancer Research and Treatment*. 2019 Jun 7;175(3):775–9.
20. Suri G, Chandiwana D, Lee A, Mistry R. Cost-effectiveness Analysis of Ribociclib plus Letrozole versus Palbociclib plus Letrozole in the United Kingdom. *Journal of Health Economics and Outcomes Research*. 2019;6(2):20–31.
21. Buehler AM, Castilho G, Dionne P-A, Stefani S. 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. *Therapeutic Advances in Medical Oncology*. 2021 Apr 16;13: 1–16.
22. Avxentyev NA, Lubennikova E V., Frolov MY. Pharmacoeconomic analysis of using cyclin-dependent kinase 4 and 6 inhibitors in the first line treatment of HR-positive HER2-negative advanced breast cancer. *FARMAKOEKONOMIKA Modern Pharmacoeconomic and Pharmacoepidemiology*. 2020 Feb 18;12(4):279–90.

23. Wang Y, Rui M, Guan X, Cao Y, Chen P. Cost-Effectiveness Analysis of Abemaciclib Plus Fulvestrant in the Second-Line Treatment of Women With HR+/HER2- Advanced or Metastatic Breast Cancer: A US Payer Perspective. *Frontiers in Medicine* (Lausanne). 2021 Jun 2;8: 658747. 502
24. Qatar Population 2021 (Demographics, Maps, Graphs) [Internet]. [cited 2021 Dec 15]. Available from: <https://worldpopulationreview.com/countries/qatar-population> 503
25. Qatar Source: Globocan 2018 [Internet]. [cited 2020 Aug 27]. Available from: <https://gco.iarc.fr/today/data/factsheets/populations/634-qatar-fact-sheets.pdf> 504
26. Ministry of Development Planning and Statistics. Qatar Second National Development Strategy 2018–2022 [Internet]. [cited 2021 Oct 02]. Available from: <https://www.psa.gov.qa/en/knowledge/Documents/NDS2Final.pdf> 505
27. National Center for Cancer Care and Research [Internet]. [cited 2021 Aug 27]. Available from: <https://www.hamad.qa/EN/Hospitals-and-services/NCCCR/Pages/default.aspx> 506
28. Tan-Torres Edejer T, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans DB, Murray DB, Murray CJL editors G. WHO Making choices in health: WHO guide to cost-effectiveness analysis. 2003. 507
29. International Monetary Fund World Economic Outlook. World GDP per capita Ranking 2020 StatisticsTimes.com [Internet]. [cited 2021 Jan 22]. Available from: <http://statisticstimes.com/economy/projected-world-gdp-capita-ranking.php> 508
30. Briggs A, Sculpher M, Claxton K. Decision Modelling for Health Economic Evaluations. OXFORD University: Oxford University Press; 51 p. 509
31. Rugo HS, Diéras V, Gelmon KA, Finn RS, Slamon DJ, Martin M, et al. Impact of palbociclib plus letrozole on patient-reported health-related quality of life: Results from the PALOMA-2 trial. *Annals of Oncology*. 2018 Apr 1;29(4):888–94. 510
32. Fasching PA, Beck JT, Chan A, De Laurentiis M, Esteva FJ, Jerusalem G, et al. Ribociclib plus fulvestrant for advanced breast cancer: Health-related quality-of-life analyses from the MONALEESA-3 study. *Breast*. 2020 Dec 1;54:148–54. 511
33. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *British Journal of Cancer*. 2006 Sep 18;95(6):683–90. 512
34. Attema AE, Brouwer WBF, Claxton K. Discounting in Economic Evaluations. Vol. 36, *Pharmacoeconomics*. Springer International Publishing; 2018. p. 745–58. 513
35. Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic Evaluation in Clinical Trials. 2nd ed. Oxford University Press; 2015. 514
36. Mason JM, Mason AR. The generalisability of pharmacoeconomic studies: Issues and challenges ahead. Vol. 24, *Pharmacoeconomics*. Pharmacoeconomics; 2006. p. 937–45. 515