pan-Canadian Oncology Drug Review
Initial Economic Guidance Report

Palbociclib (Ibrance) for Advanced Breast Cancer

May 5, 2016

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by **Pfizer Canada Inc.** compared palbociclib used in combination with letrozole to letrozole alone for the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer (ER+/HER2- ABC) as initial endocrine-based therapy for their metastatic disease. A network meta-analysis was conducted to compare palbociclib used in combination with letrozole to other aromatase inhibitors (AIs), anastrozole, tamoxifen, or exemestane.

Table 1. Submitted Economic Model

Funding Request In combination with letrozole, for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease	This aligns with the patient population of postmenopausal women with ER+/HER2- ABC
Type of Analysis	CEA/CUA
Type of Model	Partitioned-survival model
Comparator	Base-case analysis was performed for letrozole alone; sensitivity analysis included letrozole, anastrozole, exemestane and tamoxifen.
Time Horizon	10 years
Perspective	Publicly funded health care system in Canada
Cost of palbociclib	**Palbociclib costs $297.62 per 75 mg, 100 mg, and 125 mg capsule.** At the recommended dose of 125 mg once daily for 21 days followed by 7 days off treatment, palbociclib costs o $297.62 per day at the list price and $[redacted] at the confidential price (*The cost of palbociclib is based on a confidential price submitted by the manufacturer and cannot be disclosed to the public according to the pCODR Disclosure of Information Guidelines*.) o $6,250 per 28-day course at the list price and $[redacted] at the confidential price (*The cost of palbociclib is based on a confidential price submitted by the manufacturer and cannot be disclosed to the public according to the pCODR Disclosure of Information Guidelines*.) The submitted economic model used the confidential price for palbociclib.
Cost of letrozole (*Based on Ontario Drug Benefit)*	**Letrozole costs $1.378 per 2.5 mg tablet.** At the recommended dose of 2.5 mg once daily for 28 days, letrozole costs o $1.378 per day

	o $38.58 per 28-day course
Cost of comparators used in sensitivity analyses (*Based on Ontario Drug Benefit)*	**Anastrozole costs $1.2729 per 1 mg tablet.** At the recommended dose of 1 mg once daily for 28 days, anastrozole costs o $1.2729 per day o $35.6412 per 28-day course **Exemestane costs $1.3263 per 25 mg tablet.** At the recommended dose of 25 mg once daily for 28 days, exemestane costs o $1.3263 per day o $37.1364 per 28-day course **Tamoxifen costs $0.3500 per 20 mg tablet.** At the recommended dose of 20 mg once daily for 28 days, tamoxifen costs o $0.35 per day o $9.80 per 28-day course
Model Structure	The model was comprised of 3 health states: pre-progression, progression (or post-progression), and death. Transitions between these health states were driven by the PALOMA-1 trial progression-free survival (PFS) and overall survival (OS) data.
Key Data Sources	The efficacy and safety parameters were based on the PALOMA-1 trial. Various statistical methods for extrapolating survival beyond the trial period were considered.

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate, as it reflects standard treatments used in clinical practice However, the CGP noted that various AIs are available for initial treatment in ER+/HER2- disease, including anastrozole, exemestane and letrozole. PALOMA-1 compares palbociclib +letrozole to letrozole alone.

- Relevant issues identified included:
  - The CGP concluded that there may be a net overall clinical benefit to the combination of palbociclib and letrozole compared with letrozole alone in the treatment of postmenopausal women with ER+/HER2- ABC who have not received any prior treatment for metastatic disease.
  - The CGP had concerns about the quality of the study given that it was a small phase 2 study with many protocol amendments and deviations. The assessment of generalizability of evidence is limited to the patient population studied and evidence from PALOMA-1.
  - The study design of PALOMA-1 also did not explore the role of combining palbociclib with other endocrine therapies.
  - With an absolute improvement in PFS of 10 months, the magnitude of benefit is both statistically and clinically meaningful. There was no significant difference in median OS, but the study was underpowered for this endpoint.
  - Although the most common side effects experienced with palbociclib and letrozole in this trial are not life threatening, they do require monitoring by an experienced health care team familiar with the toxicities associated with this combination, as a higher incidence of adverse

events (e.g., grade 3/4 neutropenia potentially leading to febrile neutropenia) may occur in an unselected non-clinical trial population.
- The only patient reported outcome was pain, there was no difference observed between the two groups.
- There were no reported quality of life parameters in this study.

Summary of patient input relevant to the economic analysis
Patients who have experience with palbociclib considered the following to be advantages to palbociclib: the treatment helped to stabilize and control their disease. Respondents also reported their ability to live life productively with an excellent quality of life. The key adverse effects experienced by these respondents included: low white blood cell count, and more mild adverse effects such as: fatigue, febrile neutropenia, hair thinning, runny nose, mouth sores, and diarrhea. Out of the seven respondents, most respondents were able to tolerate these side effects, while others had to reduce their dosage of palbociclib. Respondents were also asked about the impact of drug administration, and commented on the ease of the oral dosage and appreciated having a break of one week on the treatment.
The economic evaluation took into consideration both PFS and quality of life. Yet the quality of life data was derived from the literature as it was not reported in PALOMA-1. The economic evaluation also took into account the dis-utilities related with the sides effects of the treatments.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for palbociclib which are relevant to the economic analysis:

Clinical factors:
- Indication creep to patients previously treated for metastatic disease
- Monthly monitoring and blood work for neutropenia

Economic factors:
- Large number of patients
- High cost of drug relative to currently available oral treatments

If recommended for funding, PAG is seeking guidance on the appropriateness of adding palbociclib for patients who are already on letrozole but not yet progressed or switching patients who are already on other AIs but not yet progressed to palbociclib plus letrozole.

PAG is seeking information on the generalizability of data for the use of plabociclib in combination with other AIs.

PAG recognizes that there may not be data on the use of palbociclib plus letrozole in patients who have been previously treated for metastatic disease with other AIs but indicated there may be pressure from oncologists and patients to use palbociclib plus letrozole as second-line.

The high cost and large potential budget impact of palbociclib is a barrier to implementation.

The economic evaluation took into consideration the relevant factors.

1.3 Submitted and EGP Reanalysis Estimates

The submitted and EGP reanalysis estimates are based on the submitted confidential price of palbociclib and based on a comparison of palbociclib plus letrozole compared with letrozole. Given the limitations and great uncertainty in the results presented through the indirect comparison for palbociclib plus letrozole versus anastrozole, tamoxifen, and exemestane, the EGP did not provide re-analysis estimates for these comparisons. Please see Section 7 of the Clinical Guidance Report for details on the critical appraisal of the presented network meta-analysis.

Table 2. Submitted base case and EGP re-analysis estimates

Estimates	Submitted	EGP Reanalysis: lower and upper bounds
ICER estimate ($/QALY), range/point	$192,992	$188,340 and $530,290
ΔE (QALY), range/point	0.680	0.324 and 0.594
ΔE (LY), range/point	0.475	0.280 and 0.431
ΔC ($), range/point	$131,161	$131,161 and $171,814

The main assumptions and limitations with the submitted economic evaluation were:

- Clinical uncertainty of PALOMA-1, the EGP and CGP had concerns about the quality of the study given that it was a small phase 2 study and that there were many study amendments.
- The cost in the post-progression state and the duration of active therapy in the post-progression state, respectively, are the main cost drivers in the economic evaluation and both were not appropriately accounted for.
    - Post-progression costs are greater for the letrozole group and for all other comparators used in the sensitivity analyses, than in the palbociclib plus letrozole group. This is mainly due to the fact that there is a greater observed benefit in PFS in the palbociclib plus letrozole group compared with comparators, yet, there is no observed significant benefit in terms of OS. For this reason, patients in the palbociclib plus letrozole group remain in the post-progression state for a shorter period of time, and so, they will receive active therapy, chemotherapy, and best supportive care (BSC) for a shorter period when compared with all other comparators. In the submitted economic evaluation, it is assumed that active therapy includes 42% of patients receiving exemestane plus everolimus, which has a high monthly cost ($5,540.46). This is the factor that has the largest impact on the submitted ICERs.
    - The EGP and CGP felt the duration of active therapy following progression in patients treated with palbociclib plus letrozole and letrozole alone should be at least similar.
- Furthermore, a chart review was used to inform the proportion of patients receiving different post-progression treatments. Yet no distinction was made by palbociclib plus letrozole and letrozole groups. From a clinical perspective, compared to the palbociclib plus letrozole group, the CGP felt more patients treated with letrozole would receive best supportive care (BSC) and thus a smaller proportion would receive active therapy in the post-progression state.
- The submitted costs of imaging were based on physician claims only not the total cost of imaging.
- As quality of life was not reported in PALOMA-1, health state utility values to inform the economic evaluation were derived from the literature.

Detailed Highlights of the EGP Reanalysis

In summary, the key assumptions that have the most impact on the results of the economic evaluation are: the types and duration of treatments in the post-progression state, as well as

different treatment pathways between groups, such as the proportion of patients receiving active therapy versus BSC. The model provided by the submitter did not allow changing of these parameters; however, the EGP performed several re-analyses, with results presented in Table 3.

As the economic evaluation was a partitioned-survival model, the duration of active therapy in the post-progression state was considered a function of the PFS and the OS estimates and not on the actual or most plausible clinical treatment pathway. This underestimates the duration of active therapy in the palbociclib plus letrozole group, and subsequently, the post-progression cost for this group. As the model did not allow reanalyses by modifying these parameters, the EGP applied three changes.

Reanalyses were conducted to account for the following parameters:

- **Survival Assumptions:** Changing the survival assumptions in the economic evaluation (parametric curves, extrapolation method using hazard ratios from the PALOMA-1 trial)
- **Cost of Post-progression Active Therapy:** As everolimus plus exemestane is the most costly treatment in post-progression, it was assumed all patients in both arms (100%) would receive active therapy with everolimus plus exemestane.
- **Utilities:** There was uncertainty related to differences in treatment arms for utilities. Dis-utilities were also not modifiable in the submitted model. Therefore, to account for uncertainty related to utilities as well as account for the higher toxicity profile in the palbociclib plus letrozole versus letrozole alone group, the utility associated with treatment with palbociclib plus letrozole was decreased or made equal to the utility associated with treatment with letrozole alone. Furthermore, as the duration of active therapy and BSC were not modifiable and patients treated with letrozole had a longer duration of active therapy than palbociclib plus letrozole, the post-progression utility associated with active therapy was set to that of BSC.
- **Incremental Cost of Post-progression Active Therapy:** The scenario where there is no difference between groups in term of the costs of post-progression active therapy was conducted, as although both the EGP and CGP expected a higher post-progression cost in the palbociclib plus letrozole group, resulting estimates did not provide this result. Therefore, resulting incremental costs (ΔC) were reduced by $34,112, the difference of mean post-progression cost between the palbociclib plus letrozole and the letrozole alone group in the submitted base case estimate.

Table 3. EGP's Reanalysis for the Best Case Estimate

Description of Reanalysis	ΔC	ΔE (PF-LYs)	ΔE (LYs)	ΔE (QALYs)	ICER ($/QALY)	Δ from baseline ICER
Baseline (Submitter's best case)	**$131,161**	**1.290**	**0.475**	**0.68**	**$192,992**	**--**
LOWER BOUND						
Survival Assumptions: Log-logistic parametric curves used for OS and PFS up until trial duration, after which treatment-specific event rates remain the same during follow-up (extrapolated benefit)	$125,636	1.287	0.431	0.661	$190,161	-$2,831
Utilities: palbociclib plus letrozole group to have the same utility as the letrozole group in the pre-progression state; BSC to have the same utility as active treatment in the post-progression state	$131,161	1.290	0.475	0.602	$217,822	$24,883

Costs: The cost per cycle of active therapy post-progression set to the monthly cost of everolimus plus exemestane ($7,340)	$117,652	1.290	0.475	0.680	$173,113	-$19,879
Best case estimate of above three parameters	**$111,879**	**1.287**	**0.431**	**0.594**	**$188,340**	**-$4,652**
UPPER BOUND						
Survival Assumptions: Estimating survival using the hazard ratios from PALOMA-1 for trial duration and follow-up (retained benefit)	$121,829	0.885	0.280	0.453	$268,736	$75,744
Utilities: palbociclib plus letrozole group to have decreased utility compared with the letrozole group in the pre-progression state; BSC to have the same utility as active treatment in the post-progression state	$131,161	1.290	0.475	0.527	$248,816	$55,824
Costs: Resulting incremental costs (ΔC) were reduced by $34, 112, the difference of mean post-progression cost between the palbociclib plus letrozole and letrozole alone group in the submitted base case estimate.	$165,372	1.290	0.475	0.68	$243,049	$50,057
Best case estimate of above three parameters (HR with retained benefit)	**$171,814**	**0.885**	**0.280**	**0.324**	**$530,290**	**$337,298**

1.4 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include the estimated market share as well as the proportion of patients eligible for provincial coverage. Increasing the proportion of patients eligible for provincial coverage and increasing the number of patients receiving first-line palbociclib increases the budget impact.

1.5 Conclusions

The EGP's best estimate of ΔC and ΔE for palbociclib when compared to letrozole is:

- Between $188,340/QALY and $530,290/QALY. The wide range is due to the large amount of clinical uncertainty.
- Within this range, the best estimate would likely be $243,049/QALY, corresponding to the scenario adjusting for the incremental difference between mean post-progression costs for palbociclib plus letrozole and letrozole alone.
- The extra cost of palbociclib plus letrozole is between $111,879 and $171,814. The factor that most influences cost is the duration of post-progression active therapy.
- The extra clinical effect of palbociclib plus letrozole is between 0.324 and 0.594. The factor that most influences effectiveness are the survival assumptions.

Overall conclusions of the submitted model:

- Though the submitted model included many appropriate assumptions, there are still some assumptions that are not concordant with clinical practice, such as: assumptions around the duration of post-progression active therapy and different clinical pathways based on the initial (first line) treatment with palbociclib plus letrozole or letrozole alone. These are major factors that substantially affect the ICURs of this economic evaluation.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Breast Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of palbociclib (Ibrance) for advanced breast cancer. A full assessment of the clinical evidence of palbociclib (Ibrance) for advanced breast cancer is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from this publicly available Guidance Report.

This Initial Economic Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Economic Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Economic Guidance Report will supersede this Initial Economic Guidance Report.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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