pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Palbociclib (Ibrance) for Advanced Breast Cancer – Resubmission

November 21, 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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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 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 o $6,250 per 28-day course at the list price
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 Phase III PALOMA-2 trial data on PFS and Phase II PALOMA-1 on OS.
Key Data Sources	The efficacy and safety parameters were based on both PALOMA-1 and PALOMA-2 trials. Various statistical methods for extrapolating survival beyond the trial period were considered.
PFS – progression free survival; OS – overall survival	

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 and PALOMA-2 compared palbociclib plus letrozole to letrozole alone and to letrozole plus placebo, respectively. Relevant issues identified included:

- The CGP concluded that there is 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. Based on the preliminary results of PALOMA-2, a 10 month median PFS benefit was achieved, as was demonstrated in PALOMA-1. The median PFS was higher in PALOMA-2 compared to PALOMA-1, for both treatment arms. This difference can be accounted for in PALOMA-2 since there was a larger patient population in this randomized placebo-controlled trial, and the PFS of 14.5 months demonstrated in the control arm of letrozole was more comparable to previous reported clinical trials for AI first-line therapy in advanced ER+/HER2- breast cancer.
- The CGP had concerns about the quality of the PALOMA-1 study given that it was a small phase 2 study with many protocol amendments and deviations. However, as noted by the CGP, these results were confirmed by the PALOMA-2 study, a randomized phase 3 trial with a larger population. The assessment of generalizability of evidence is limited to the patient population studied and evidence from PALOMA-1 and PALOMA-2.
- The study design of PALOMA-1 and PALOMA-2 also did not explore the role of combining palbociclib with other endocrine therapies.
- With an absolute improvement in PFS of 10 months confirmed by both studies, the magnitude of benefit is both statistically and clinically meaningful. There was no significant difference in median OS, but the PALOMA-1 study was underpowered for this endpoint. In addition, no OS conclusions were made on PALOMA-2, due to the immaturity of the data.
- The CGP noted that the addition of palbociclib to letrozole in the treatment of first-line ER+/HER2- metastatic breast cancer patients will require closer clinical monitoring compared to letrozole alone, based on the safety and toxicity of the combination treatment. Specifically, myelosuppression with neutropenia and a risk of febrile neutropenia was noted in PALOMA-2. Clinical medical education will be required of treating oncologists as to the adverse events and appropriate monitoring and treatment of them when palbociclib is added to the first-line letrozole therapy.

- There were no reported quality of life parameters in this study except for pre-progression state.
- The CGP concluded that, within the Canadian context, based on these results of both PALOMA-1 and PALOMA-2, it is likely that the combination of palbociclib and letrozole will replace single agent first-line endocrine therapy in the metastatic setting. In the interim, based on these results of PALOMA-1 and PALOMA-2, it is possible the use of letrozole in the adjuvant setting for ER+ post-menopausal women may decrease, as prior use of letrozole may be a barrier to receiving the combination of letrozole and palbociclib in the advanced treatment setting. However, the decision of treatment choice of endocrine therapy in the adjuvant setting may be mitigated by allowing the treatment coupling of palbociclib with any endocrine therapy (tamoxifen, any AI, fulvestrant) in the treatment of first or second-line ER+/HER2- ABC patients. In fact, this is now allowed in the European Union, while recognizing that clinical evidence only exists for combining palbociclib with letrozole or with fulvestrant, based on the randomized trials of PALOMA-1, 2 and 3.

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 for the post-progression state and from PALOMA-2 for the pre-progression state. 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:

- Potentially large budget impact given the high number of patients eligible for treatment
- The cost-effectiveness of palbociclib with letrozole combination therapy compared with letrozole monotherapy and monotherapy with other aromatase inhibitors
- Additional costs to the health system related to monthly monitoring and bloodwork for neutropenia and other adverse events associated with palbociclib, which is not required with letrozole monotherapy

Summary of registered clinician input relevant to the economic analysis
Registered clinicians noted that early benefits may translate to longer disease control but the overall survival benefits may be impacted by downstream treatments and optimal treatment sequence is unknown. Registered clinicians considered the additional cost of an add-on therapy and the additional toxicities associated with palbociclib.

1.3 Submitted and EGP Reanalysis Estimates

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

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

Estimates	Submitted	EGP Reanalysis: lower and upper bounds
ICER estimate ($/QALY), range/point	$310,007	$295,925/QALY and $745,785/QALY
ΔE (QALY), range/point	0.641	0.257 and 0.641
ΔE (LY), range/point	0.475	0.232 and 0.475
ΔC ($), range/point	$198,623	$174,484 and $227,517

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

- The cost in the post-progression state and the duration of active therapy (AT) in the post-progression state, respectively, are the main cost drivers in the economic evaluation and were not appropriately accounted for.
    - Post-progression costs are greater in the letrozole group and 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 AT, chemotherapy, and BSC for a shorter period when compared with all other comparators. In the submitted economic evaluation, it is assumed that AT includes 43% 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 duration of AT, the EGP and CGP felt the duration of AT 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 AT 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 in PALOMA-2 was only reported for pre-progression states, the health-related quality of life utilities in post-progression state to inform the economic evaluation were derived from the literature.

1.4 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 AT

versus BSC. The model provided by the submitter did not allow changing of these parameters, with the exception of duration of treatments post-progression; 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 AT 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 AT in the palbociclib plus letrozole group, and subsequently, the post-progression cost for this group.

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 and PALOMA-2 trials)
- **Cost of Post-progression AT:** As everolimus plus exemestane is the most costly treatment in post-progression, it was assumed all patients in both arms (100% or 75%) would receive active therapy with everolimus plus exemestane.
- **Utilities:** Dis-utilities for adverse events were not modifiable separately from utilities 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 made equal to the utility associated with treatment with letrozole alone. Furthermore, as the duration of AT and BSC were not modifiable and patients treated with letrozole had a longer duration of AT than palbociclib plus letrozole, the post-progression utility associated with AT was set to that of BSC.
- **Incremental Cost of Post-progression state:** The scenario where there is no difference between groups in term of the costs of post-progression AT was conducted, although both the EGP and CGP expected a higher post-progression cost in the palbociclib plus letrozole group. Therefore, incremental cost of post-progression AT and BSC were set to 0, so the difference of mean post-progression cost between the palbociclib plus letrozole and letrozole alone group will be 0.

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)	**$198,623**	**1.192**	**0.475**	**0.641**	**$310,007**	--
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) (highly optimistic)	$201,535	1.113	0.473	0.616	$327,303	$17,296
Utilities: palbociclib plus letrozole group to have the same utility as the letrozole group in the pre-progression state = 0.74; BSC to have the same utility as active treatment in the post-progression state = 0.496	$198,623	1.192	0.475	0.590	$336,649	$26,642

Description of Reanalysis	ΔC	ΔE (PF-LYs)	ΔE (LYs)	ΔE (QALYs)	ICER ($/QALY)	Δ from baseline ICER
Costs: The cost per cycle of active therapy post-progression set to the monthly cost of everolimus plus exemestane ($7,340)	$189,688	1.192	0.475	0.641	$295,925	-$14,082
Best case estimate of above three parameters	**$193,526**	**1.113**	**0.473**	**0.563**	**$343,935**	**$33,928**
UPPER BOUND						
Survival Assumptions: Log-logistic parametric curves used for OS and PFS up until trial duration, after which accrued survival advantage is retained, but subsequent rates are assumed to be the same in both treatment arms. (retained benefit)	$174,484	0.662	0.232	0.369	$472,856	$162,849
Utilities: palbociclib plus letrozole group to have the same utility compared with the letrozole group in the pre-progression state=0.71; BSC to have the same utility as active treatment in the post-progression state=0.496	$198,623	1.192	0.475	0.554	$358,525	$48,518
Costs: the difference of mean post-progression cost between the palbociclib plus letrozole and letrozole alone group = 0 (costs AT and BSC = 0)	$227,517	1.192	0.475	0.641	$354,941	$44,934
Best case estimate of above three parameters (HR with retained benefit)	**$191,624**	**0.662**	**0.232**	**0.257**	**$745,785**	**$435,778**

Note: As per submitter description: extrapolated benefit assumption: treatment-specific event rate remains the same during the follow-up (highly optimistic scenario); retained benefit assumption: accrued survival advantage is retained, but subsequent rates are assumed to be the same in both treatment arms. The rates of the comparator arm will then be used.

1.5 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. Increase the proportion of patients eligible for provincial coverage and increasing the number of patients receiving first-line palbociclib increases the budget impact.

1.6 Conclusions

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

- Between $295,925/QALY and $745,785/QALY.
- Within this range, the best estimate would likely be $327,303/QALY, corresponding to the scenario of 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).
- The extra cost of palbociclib plus letrozole is between $174,484 and $227,517. The factor that most influence cost is the duration of post-progression AT.
- The extra clinical effect of palbociclib plus letrozole is between 0.257 and 0.641 QALY. The factor that influence 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 or are inappropriately supported by the current evidence, such as: survival benefits after the trial period, assumptions around the duration of post-progression AT 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*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

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. .

REFERENCES

1. Beauchemin C, Letarte N, Mathurin K, Yelle L, Lachaine J. A global economic model to assess the cost-effectiveness of new treatments for advanced breast cancer in Canada. J Med Econ. 2016:1-11. Epub 2016/02/07.

2. Marchetti M, Caruggi M, Colombo G. Cost utility and budget impact of third-generation aromatase inhibitors for advanced breast cancer: a literature-based model analysis of costs in the Italian National Health Service. Clin Ther. 2004;26(9):1546-61. Epub 2004/11/09.

3. Lux MP, Hartmann M, Jackisch C, Raab G, Schneeweiss A, Possinger K, et al. Cost-utility analysis for advanced breast cancer therapy in Germany: results of the fulvestrant sequencing model. Breast Cancer Res Treat. 2009;117(2):305-17. Epub 2009/01/09.

4. Lindgren P, Jonsson B, Redaelli A, Radice D. Cost-effectiveness analysis of exemestane compared with megestrol in advanced breast cancer: a model for Europe and Australia. Pharmacoeconomics. 2002;20(2):101-8. Epub 2002/03/13.