pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Palbociclib (Ibrance)

Submitted Reimbursement Request:
In combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer whose disease progressed after prior endocrine therapy, pre- or perimenopausal women must also be treated with a luteinizing hormone releasing hormone (LHRH) agonist.

Submitted By: Pfizer Canada Inc.	**Manufactured By:** Pfizer Canada Inc.
NOC Date: May 19, 2017	**Submission Date:** September 28, 2018
Initial Recommendation: March 7, 2019	**Final Recommendation:** May 3, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Palbociclib costs $253.90 per unit. At the recommended dose of 125 mg once daily for 21 consecutive days, followed by seven days off treatment, palbociclib costs $5,332.16 per 28-day cycle. Fulvestrant costs $582.90 per unit. At the recommended dose of 500 mg on days 0, 14, 28, and every 28 days thereafter, fulvestrant costs $582.90 per day, $2,331.60 for the first cycle, and $1,165.80 for subsequent cycles.

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC recommends reimbursement of palbociclib (Ibrance) in combination with fulvestrant only if the following conditions are met:

- Cost-effectiveness is improved to an acceptable level
- Feasibility of adoption (budget impact) is addressed

Reimbursement should be in combination with fulvestrant for the treatment of patients with HR-positive, HER2-negative locally advanced (aBC) or metastatic breast cancer (mBC) whose disease has progressed after prior endocrine therapy. Patients should have good performance status and can be of any menopausal status (Perimenopausal and premenopausal women must be treated with an LHRH agonist). Treatment should continue until unacceptable toxicity or disease progression.

pERC made this Recommendation because it was satisfied that compared with fulvestrant monotherapy, there is a net clinical benefit of palbociclib plus fulvestrant based on a statistically significant and clinically meaningful improvement in progression-free survival (PFS), a manageable toxicity profile, and ability to maintain quality of life (QoL). However, the Committee's assessment of net clinical benefit was tempered by a lack of evidence for an improvement in overall survival (OS). pERC agreed that palbociclib plus fulvestrant aligns with the patient values offering a treatment alternative to chemotherapy that delays disease progression and maintains QoL.

	In addition, the Committee considered evidence provided through an indirect treatment comparison with everolimus plus exemestane and with other relevant aromatase inhibitors. pERC concluded that there may be a net clinical benefit of palbociclib plus fulvestrant compared with both treatment options; however, there is considerable uncertainty concerning the magnitude of benefit due to the lack of direct comparative evidence between these agents, particularly with the comparison to everolimus plus exemestane. When compared with everolimus plus exemestane, pERC noted that palbociclib plus fulvestrant likely has a more manageable safety profile, which meets patient values. pERC concluded that, at the submitted price, palbociclib plus fulvestrant is not cost-effective compared with fulvestrant monotherapy or with everolimus plus exemestane. pERC also highlighted that the submitted budget impact of palbociclib plus fulvestrant was very underestimated and the actual budget impact would be substantial. Therefore, pERC had concerns about the capacity of jurisdictions to implement the therapy.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost- Effectiveness and Budget Impact** Given that there is a net clinical benefit of palbociclib plus fulvestrant compared with fulvestrant monotherapy, and that there may be a net clinical benefit of palbociclib plus fulvestrant compared with everolimus plus exemestane, jurisdictions will need to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and affordability of palbociclib plus fulvestrant to an acceptable level. pERC further noted that the incremental benefit between palbociclib plus fulvestrant and everolimus plus exemestane is small, and the magnitude of this benefit is unclear. **Optimal Sequencing of Palbociclib Plus Fulvestrant and Other Therapies is Unknown** pERC concluded that the optimal sequencing of palbociclib plus fulvestrant and other therapies now available for the treatment of patients with HR-positive, HER2-negative, locally advanced breast cancer (aBC) or metastatic breast cancer (mBC) whose disease progressed after prior endocrine therapy is currently unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatment with palbociclib plus fulvestrant. pERC noted that jurisdictions may want to consider developing a common approach to treatment sequencing of all available drugs in this setting. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

Breast cancer is the most common cancer in women in Canada and the second most common cause of cancer mortality in Canadian women. Hormone receptor (HR)-positive, human epidermal growth factor receptor 2-negative (HER2) breast cancer represents approximately 65% to 70% of all breast cancers. pERC noted that the goals of treatment for patients with aBC or mBC are primarily palliative—namely, to prolong life while maintaining or improving QoL. For those patients who do not receive a cyclin-dependent kinase (CDK) inhibitor plus letrozole in the first-line setting, the main competing alternative second-line hormonal treatments are exemestane with or without everolimus, tamoxifen, or single-agent fulvestrant (fulvestrant is currently only accessible through private insurance or out-of-pocket payment). pERC acknowledged and agreed with the pCODR Clinical Guidance Panel (CGP) that everolimus plus exemestane has a clinical benefit, but is also associated with considerable toxicity. Overall, pERC considered there to be a need for new and effective therapies for patients with aBC or mBC that provide improvements in patient survival, have more favourable toxicity profiles, and improve QoL.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of one phase III, international, multi-centre, randomized, double-blind, placebo-controlled trial, PALOMA-3, that compared palbociclib plus fulvestrant with fulvestrant monotherapy in women with HR-positive, HER2-negative, locally aBC or mBC whose disease had progressed after prior endocrine therapy regardless of menopausal status. pERC noted that fulvestrant monotherapy is not reimbursed publicly for this indication in Canadian jurisdictions. PALOMA-3 reported a statistically significant improvement in PFS in favour of palbociclib plus fulvestrant compared with fulvestrant. pERC also noted that neither a statistically significant nor a clinically meaningful improvement in OS was observed at this time in the PALOMA-3 trial. pERC discussed the available QoL data from the PALOMA-3 trial and noted that QoL for patients taking palbociclib plus fulvestrant did not decline more than it did for those taking fulvestrant. In the absence of OS data and improvement in QoL, pERC had a robust discussion of the clinical significance of an improvement in PFS in aBC or mBC. While multiple opinions were expressed, the majority of pERC members agreed that the delay in progression of disease is a meaningful end point in this clinical setting; therefore, a majority of Committee members agreed that the PFS benefit observed in PALOMA-3 is clinically meaningful. This was in alignment with the conclusions of the CGP and input from registered clinicians and two patient groups. pERC discussed the toxicity profile of palbociclib plus fulvestrant and noted that there were more frequent toxicities compared with fulvestrant monotherapy, including grade 3 and 4 adverse events (AEs), such as neutropenia, leukopenia, anemia, and thrombocytopenia. A higher incidence of infections was also reported in the palbociclib-plus-fulvestrant group. However, slightly more serious AEs occurred in the fulvestrant group. pERC noted that the AEs with palbociclib plus fulvestrant could be managed in clinical practice through dose adjustments. Overall, pERC concluded that there is a net clinical benefit of palbociclib plus fulvestrant compared with fulvestrant monotherapy based on the statistically significant and clinically meaningful improvements in PFS, no observed detriment in QoL, and manageable toxicity profile. In making this conclusion, the Committee's deliberations were tempered by the lack of evidence demonstrating an improvement in OS.

pERC noted that the submitter provided a network meta-analysis (NMA) that compared palbociclib plus fulvestrant with everolimus plus exemestane or other relevant aromatase inhibitors (AIs). pERC acknowledged and agreed with the CGP's conclusions that the efficacy and safety of most single-agent AIs are similar and agreed that palbociclib plus fulvestrant is likely more effective than an AI monotherapy. This was demonstrated in the favourable hazard ratios reported for palbociclib plus fulvestrant in the NMA. pERC further noted that palbociclib plus fulvestrant is likely similar in efficacy with everolimus plus exemestane, as supported by the hazard ratios generated through the NMA. Furthermore, input from registered clinicians highlighted that toxicities with everolimus plus exemestane (e.g., mucositis, nausea, diarrhea, and rash) make it a less favourable choice for patients and clinicians than palbociclib plus fulvestrant. The CGP's conclusions also highlighted the more favourable toxicity profile with palbociclib plus fulvestrant when compared with everolimus plus exemestane. Therefore, pERC concluded that there

may be a net clinical benefit with palbociclib plus fulvestrant when compared with everolimus plus exemestane based on a more favourable toxicity profile. Likewise, notwithstanding the limitations of the indirect comparison, pERC concluded that there may be a net clinical benefit with palbociclib plus fulvestrant when compared with other single-agent AIs.

pERC discussed the generalizability of the PALOMA-3 trial results in patients with HR-positive, HER2-negative aBC or mBC. Although the PALOMA-3 trial only included patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1, pERC noted that the decision to restrict treatment based on PS should be left to the treating oncologist. Therefore, pERC concluded that patients with a good PS should be eligible for palbociclib plus fulvestrant. pERC also stated that age should not be a restrictive factor for eligibility, as younger patients may be considered frail (e.g., comorbidities may render younger patients too frail for treatment). Therefore, pERC concluded that the ability of patients to tolerate treatment should be determined by the treating oncologist. Furthermore, pERC agreed it would be reasonable to treat the rare male patients with HR-positive, HER2-negative mBC and patients with double equivocal HER2 disease (who are considered to be HER2 negative). However, pERC agreed that the PALOMA-3 trial is not generalizable to patients with extensive symptomatic visceral metastases and uncontrolled central nervous system (CNS) metastases.

pERC deliberated upon the cost-effectiveness of palbociclib plus fulvestrant and concluded that it is not cost-effective when compared with fulvestrant monotherapy or everolimus plus exemestane in patients with HR-positive, HER2-negative aBC or mBC. pERC considered a number of contributing factors that led to a substantial increase in the incremental cost-effectiveness ratio (ICER). For the comparison with fulvestrant and other relevant AIs, pERC noted that the assumption of long-term OS and PFS benefit had the biggest impact on the ICER. Given the absence of long-term PFS and OS data and lack of a demonstrated OS benefit, the pCODR Economic Guidance Panel (EGP) explored several scenarios for extrapolating long-term PFS and OS. The EGP also explored the impact of dose intensity, shortening the time horizon, and alternative utility values from the literature, all of which had smaller impacts on the ICER. When these factors were combined, the EGP's ICER increased.

pERC further discussed the cost-effectiveness analysis when compared with everolimus plus exemestane. pERC noted that the results of the NMA, conclusions of the CGP, and input by registered clinicians confirmed the absence of an incremental benefit in PFS or OS between the two combinations. Based on this, pERC agreed with the EGP reanalysis setting the hazard ratio for PFS and OS to 1. pERC also acknowledged that a meaningful difference in toxicity profile is expected between the two combination agents, in favour of palbociclib plus fulvestrant. pERC acknowledged that it was unclear how well this difference may have been captured by the QoL instruments used in the PALOMA-3 trial. To control for potential differences in the methodology of collecting utility values (PALOMA-3 and literature values), the EGP explored the use of utility estimates from the literature for both treatment groups. pERC further noted that the ICER was very sensitive to the dose intensity. While the PALOMA-3 trial was used to estimate the dose intensity for palbociclib, full-dose intensity was used for everolimus. Given the anticipated toxicity with everolimus plus exemestane, it is not unreasonable that a dose intensity below 100% would be expected for this regimen. The EGP explored the impact of having the same dose intensity for both treatment groups. This had the largest impact on the ICER. When these factors were combined, the ICER increased substantially. Overall, pERC concluded that palbociclib plus fulvestrant is not cost-effective when compared with fulvestrant or everolimus plus exemestane. pERC concluded that a substantial price reduction will be needed to improve the cost-effectiveness of palbociclib plus fulvestrant.

Following the posting of the pERC Initial Recommendation and in response to feedback from the submitter, the EGP presented the probabilistic reanalyses for the upper and lower bounds of both comparisons (fulvestrant and everolimus plus exemestane). Based on the probabilistic analysis, the ICERs for the comparison with fulvestrant remained relatively consistent with the deterministic results. The probabilistic results, however, showed that palbociclib plus fulvestrant was dominated (more costly and less effective) by everolimus plus exemestane. pERC discussed these results and reiterated that a meaningful difference in toxicity profile is expected between the two combination agents in favour of palbociclib plus fulvestrant, although it was unclear how well this difference may have been captured by the QoL instruments used in the PALOMA-3 trial. A minority of the committee considered revising the recommendation to restrict the cost of palbociclib plus fulvestrant to be no greater than the list price for everolimus plus exemestane. Overall, pERC agreed that there is uncertainty in the magnitude of benefit anticipated through this difference in toxicity. Given that small changes in the incremental benefit can

have dramatic impacts on the ICER, as is demonstrated through the probabilistic results, pERC agreed that a substantial price reduction would be appropriate to ensure that palbociclib plus fulvestrant is cost-effective. Furthermore, the EGP provided the results of a sequential analysis where all comparators were compared. Based on this analysis and the principles of extended dominance (scenario where an ICER relative to the next less costly un-dominated intervention is greater than that of a more costly intervention or provides less benefit that this more costly intervention), everolimus plus exemestane was more cost-effective than palbociclib plus fulvestrant.

pERC considered the feasibility of implementing a reimbursement recommendation for palbociclib plus fulvestrant and highlighted a number of concerns. pERC noted that the number of patients who are expected to receive palbociclib plus fulvestrant in the second-line setting is small (given that most patients will receive a CDK inhibitor plus AI in the first-line setting); however, there is a large prevalent population that may be on everolimus plus exemestane or an AI in the first-line setting and who will be eligible for palbociclib plus fulvestrant upon progression. pERC also noted that the use of an Ontario perspective to determine the number of patients who will be eligible for public reimbursement of palbociclib plus fulvestrant may not be most representative of Canadian practice, as there is variability in the funding structures for oral agents across jurisdictions. Based on these factors, pERC agreed that the market share of palbociclib plus fulvestrant will be higher than what is depicted in the submitted budget impact analysis.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis (BIA)
- Guidance from the pCODR clinical and economic review panels
- Input from two patient advocacy groups (Rethink Breast Cancer [RBC] and Canadian Breast Cancer Network [CBCN])
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- one clinician group (Cancer care Ontario, CCO)
- PAG
- the submitter (Pfizer Canada Inc.).

The pERC Initial Recommendation was to recommend reimbursement of palbociclib (Ibrance) in combination with fulvestrant. Feedback on the pERC Initial Recommendation indicated that the manufacturer and registered clinician feedback agreed in part and PAG agreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of palbociclib (Ibrance) in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced breast cancer (aBC) or metastatic breast cancer (mBC) who progressed after prior endocrine therapy.

Studies included: Network meta-analysis to compare with appropriate comparators

The pCODR systematic review includes one phase III, international, multi-centre, randomized, double-blind, placebo-controlled trial, PALOMA-3, comparing palbociclib + fulvestrant with placebo + fulvestrant in a 2:1 ratio in women with HR-positive, HER2–negative mBC whose disease had progressed after prior endocrine therapy regardless of menopausal status.

The pCODR review also provided contextual information on a critical appraisal of the systematic review and network meta-analysis (NMA) comparing palbociclib with other therapies for HR-positive, HER2-negative aBC or mBC patients whose disease progressed after prior endocrine therapy. The results of the NMA demonstrated that palbociclib plus fulvestrant is more effective than all available single-agent AIs and similar in efficacy to everolimus plus exemestane. pERC acknowledged and agreed with the conclusions of the pCODR Clinical Guidance Panel (CGP) that the efficacy and safety of most single-agent aromatase inhibitors (AIs) is similar and that palbociclib plus fulvestrant is likely more effective than an AI monotherapy. pERC further agreed that palbociclib plus fulvestrant is likely similar in efficacy with everolimus plus exemestane. Input from registered clinicians and the CGP highlighted that toxicities with everolimus plus exemestane (e.g., mucositis, nausea, diarrhea, and rash) make it a poor choice for patients, and clinicians would prefer to use palbociclib plus fulvestrant. Therefore, pERC agreed that there may be a net clinical benefit with palbociclib plus fulvestrant when compared with everolimus plus exemestane based on a more favourable toxicity profile. Likewise, notwithstanding the limitation of making indirect comparisons, pERC agreed there may be a net clinical benefit with palbociclib plus fulvestrant when compared with other single-agent AIs.

Patient populations: Premenopausal, perimenopausal, or postmenopausal

Key eligibility criteria included that patients be women aged ≥ 18 years of any menopausal status (premenopausal, perimenopausal, or postmenopausal). Patients who were perimenopausal or premenopausal were to be treated with the luteinizing hormone-releasing hormone (LHRH) agonist

goserelin. Patients had to have an Eastern Cooperative Oncology Group ECOG Performance Status (PS) of 0 to 1. Key exclusion criteria included previous treatment with a cyclin-dependent kinase (CDK), or phosphoinositide 3-kinase (PI3K), or a mammalian target of rapamycin (mTOR) pathway inhibitor, extensive symptomatic visceral metastasis, uncontrolled brain metastases and patients at risk of life-threatening complications in the short term.

A total of 521 eligible patients were randomized in a 2:1 ratio to receive palbociclib plus fulvestrant (n = 347) or placebo plus fulvestrant (n = 174) in 28-day cycles. Randomization was stratified based on sensitivity to previous hormonal therapy, menopausal status at baseline, and presence of visceral metastases. The median age of the study participants was 57 years, with the majority of patients being younger than 65 years (75.2%), white (73.9%), or from non-Hispanic or non-Latino ethnicities (94.0%). A total of 77.9% of patients had measurable disease, with the most commonly involved disease sites being bone (75.2%), liver (39.9%), and lymph nodes (38.6%). Nearly 22% of patients in either treatment group had received more than three prior lines of therapy. Nearly 60% of the patients in both treatment groups had visceral metastases. Most patients had an ECOG PS of 0 (60% and 66% in the palbociclib-plus-fulvestrant group compared with the placebo-plus-fulvestrant group, respectively).

Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. Crossover between treatment arms was not allowed. However, patients could continue treatment as assigned at randomization beyond the time of Response Evaluation Criteria in Solid Tumors (RECIST)-defined disease progression at the discretion of the investigator if that was considered to be in the best interest of the patient and as long as no new anticancer treatment was initiated.

Key efficacy results: Statistically significant and clinically meaningful improvement in progression-free survival, but not in overall survival

The key efficacy outcome deliberated on by pERC included investigator-assessed progression-free survival (PFS), the primary end point of the study. Key secondary efficacy end points included overall survival (OS) and safety.

As of the December 5, 2014 data cut-off date, the median PFS periods were 9.2 months and 3.8 months in the palbociclib-plus-fulvestrant and placebo-plus-fulvestrant groups, respectively (hazard ratio [HR]: 0.42; 95% confidence interval [CI], 0.32 to 0.56; $P < 0.001$). The results of this analysis crossed the pre-specified efficacy boundary of alpha = 0.00135; therefore, the study was stopped early (in April 2015) for efficacy. The results of the subgroup analyses were generally consistent with the results of the primary analysis. The final analysis of the OS data was conducted after the data reached a 60% maturity (i.e., 310 deaths among 521 patients). The median OS was 34.9 months and 28.0 months for patients in the palbociclib-plus-fulvestrant and placebo-plus-fulvestrant arms, respectively (stratified hazard ratio = 0.81; 95% CI, 0.64 to 1.03; $P = 0.09$). The OS rates at three years were 50% and 41% (95% CI, 33% to 48%) in the palbociclib-plus-fulvestrant and placebo-plus-fulvestrant arms, respectively.

In the absence of OS data and improvement in quality of life (QoL), pERC had a robust discussion of the clinical significance of an improvement in PFS in aBC and mBC. While multiple opinions were expressed, the majority of pERC members agreed that the delay in progression of disease is a meaningful end point in this clinical setting. Therefore, a majority of Committee members agreed that the PFS benefit observed in PALOMA-3 is clinically meaningful.

Patient-reported outcomes: No deterioration in quality of life

Patient-reported outcomes were reported using the European Organisation for Research and Treatment of Cancer (EORTC) Qualify of Life Questionnaire–Core 30 (QLQ-C30) and the breast-specific module (QLQ-BR23). Questionnaire completion rates (completion of ≥ 1 question) were ≥ 95.8% for the EORTC QLQ-C30, and ≥ 93.8% for the EORTC QLQ-BR23 questionnaires. The QoL score was significantly higher in the palbociclib-plus-fulvestrant arm (66.1; 95% CI, 64.5 to 67.7) than in the placebo-plus-fulvestrant arm (63.0; 95% CI 60.6 to 65.3; $P = 0.0313$). No clinically meaningful difference was reported in any of the functional or symptom scales for the QLQ-C30.

No clinically meaningful differences (i.e., a minimal clinically important difference of 10 points) were observed for other QLQ-BR23 functional or symptom scales. In addition, treatment with palbociclib plus fulvestrant resulted in a statistically significant delay in deterioration of QoL (HR = 0.641; $P = 0.0065$) and

in pain (HR = 0.642; *P* < 0.001). pERC discussed the available QoL data from the PALOMA-3 trial and noted that QoL for palbociclib plus fulvestrant did not decline more than for fulvestrant.

Safety: Increased toxicity compared with fulvestrant, but manageable

As of the December 5, 2014 data cut-off date, 97.7% of patients in the palbociclib-plus-fulvestrant arm and 89.0% of those in the placebo-plus-fulvestrant arm had at least one reported adverse event (AE) (any grade). Grade 3 or 4 AEs occurred in 69.3% of patients in the palbociclib-plus-fulvestrant arm and in 18.0% of those in the placebo-plus-fulvestrant arm. The most common grade 3 or 4 AEs reported with palbociclib plus fulvestrant included: neutropenia, leukopenia, anemia, and thrombocytopenia. Serious AEs (any cause) occurred in 9.6% of the patients in the palbociclib-plus-fulvestrant arm and in 14.0% of the patients in the placebo-plus-fulvestrant arm. The results of the long-term safety analysis (April 3, 2018 data cut-off date) were consistent with those in those of the interim analysis. Discontinuation of palbociclib (or matching placebo) due to AEs was reported in 2.6% of patients receiving palbociclib plus fulvestrant and 1.7% of those receiving placebo plus fulvestrant.

pERC discussed the toxicity profile of palbociclib plus fulvestrant and noted that there were more frequent toxicities compared with fulvestrant monotherapy, including grade 3 and 4 AEs, such as neutropenia, leukopenia, anemia, and thrombocytopenia. A higher incidence of infections was also reported in the palbociclib-plus-fulvestrant group. However, slightly more serious AEs occurred in the fulvestrant group. pERC noted that the AEs with palbociclib plus fulvestrant could be managed in clinical practice through dose adjustments.

Need and burden of illness: Options with more manageable toxicities

Breast cancer is the most common cancer in women in Canada and the second most common cause of cancer mortality in Canadian women. Hormone receptor (HR)-positive, HER2–negative breast cancer represents approximately 65% to 70% of all breast cancers. pERC noted that the goals of treatment for patients with aBC or mBC are primarily palliative; namely, to prolong life while maintaining or improving QoL. pERC noted that in the first-line treatment of postmenopausal women with HR-positive, HER2–negative aBC or mBC, palbociclib plus letrozole is a standard option that has become available to most patients. Approximately 50% to 60% of patients will receive first-line CDK inhibitors. A limited number of patients who were not eligible to receive first-line palbociclib/letrozole will receive it in the second line (e.g., received nonsteroidal AI treatment for mBC before palbociclib was available, chose not to receive it, or had a contraindication to palbociclib that is no longer operative). The main competing alternative second-line hormonal treatments would therefore be exemestane with or without everolimus, tamoxifen, or single-agent fulvestrant (only accessible through private insurance or out-of-pocket payment). Overall, pERC considered there to be a need for new and effective therapies for patients with aBC or mBC that provide improvements in patient survival, have more favourable toxicity profiles, and improve QoL.

Registered clinician input: Improvement in progression-free survival is meaningful

For patients with HR-positive, HER2-negative mBC who have previously been treated with an endocrine therapy, treatment options include systemic chemotherapy, tamoxifen, and exemestane plus everolimus. Chemotherapy would be used in the minority of patients who have severe organ involvement or very rapidly progressing visceral symptomatic disease. Clinicians noted that there is an unmet need for patients treated with single-agent endocrine therapy upfront, patients who relapse on or within 12 months of finishing adjuvant endocrine therapy and need an alternative to exemestane plus everolimus, and patients exposed to a line of chemotherapy in the metastatic setting before or after progression on single-agent endocrine therapy.

According to clinicians, PFS improvement, as demonstrated in the PALOMA-3 trial, is clinically meaningful and substantially delays symptomatic deterioration and the need for chemotherapy. Although there are no data directly comparing palbociclib plus fulvestrant to exemestane plus everolimus or chemotherapy, the side effect profile of palbociclib plus fulvestrant appears more favourable than the profile normally seen with the other options. Exemestane plus everolimus is often poorly tolerated due to mucositis, nausea, diarrhea, and rash, and may particularly affect patients rarely with significant lung toxicity. One clinician observed that the hazard ratio associated with palbociclib and fulvestrant is similar to that of first-line palbociclib and letrozole, and the benefits are equally impressive. One clinician with experience using palbociclib plus fulvestrant noted that it was very tolerable in the long term and that clinical response was favourable, especially in view of the poor prognosis beyond first-line treatment.

Although first-line treatment with a palbociclib plus AI would be preferred, since the PFS benefit is greater, the availability of palbociclib plus fulvestrant allows clinicians to determine when best to treat patients with a CDK 4/6 inhibitor (as first or second-line therapy). The new drug combination would also allow treatment of premenopausal women, a group that is currently excluded from first-line palbociclib funding. Clinicians surmise that palbociclib plus fulvestrant would replace second-line AIs. In light of pre-clinical data suggesting that exemestane plus everolimus is effective after exposure to CDK4/6 inhibitors, clinicians would consider this combination (if available) after palbociclib plus fulvestrant and would prefer to reserve chemotherapy after all endocrine therapies have been exhausted.

Clinicians noted that patients with HER2 double equivocal disease would not qualify as HER2-positive according to the new American Society of Clinical Oncology/College of American Pathologists guidelines. pERC also agreed that the PALOMA-3 data can be generalized to patients with HER2 double equivocal disease (who are considered HER2-negative). Clinicians further noted that they preferred to use chemotherapy for patients with extensive, very symptomatic, and potentially life-threatening visceral disease.

PATIENT-BASED VALUES

Values of patients with HR-positive, HER2-negative metastatic breast cancer: Manage financial burden, improve quality of life

Input was received from RBC and CBCN. Based on the CBCN input, fatigue, insomnia, and pain had a significant or debilitating impact in at least 37% of patients. These same symptoms were considered to have some or moderate impact in at least 40% of patients. Patients noted that mBC affects all aspects of their lives, restricting employment and career prospects, the ability to care for children and dependents, and the ability to socially and meaningfully participate in the community. Patients mentioned other experiences, including guilt, the feeling of being a burden on caregivers, fear of death, poor body image, not knowing what functionality will be lost, fear of the impact of the loss of a parent on children, not knowing what will happen to children, the loss of support of loved ones, and marital stress or loss of fidelity and affection from their partners.

Patients noted that letrozole and tamoxifen were the most common forms of treatment they received. Fatigue was the most commonly reported side effect with these treatments (88%, n = 25/26), followed by insomnia (48%), nausea, and constipation (40% for each). Financial challenges were identified as an important issue for patients, with travel costs (48%), lost income due to work absence (44%), drug costs (28%), and parking costs (24%) being the most commonly mentioned issues. CBCN reported that the financial burden of treating and managing breast cancer directly affected whether or not the patients adhered to cancer treatments or supportive medications. Patients also noted that not qualifying for insurance at work, inability to change employers due to loss of insurance, and the prohibitive cost of new treatment options with the other financial challenges they faced. Furthermore, patients with young children faced challenges in finding child care services while they were on treatment.

Patient values on treatment: Improved progression-free survival and quality of life

Input from patients noted that long-term health outcomes were important when considering a new treatment, with 25/26 patients giving the highest score for controlling disease and 24/26 for preventing recurrence and maintaining QoL. Patients want new treatments that offer a better QoL compared with that experienced during chemotherapy or when using more toxic therapies. Patients embraced opportunities to try new treatments, even if the benefit might be as few as six months' PFS. According to RBC, all but one patient indicated that they would be willing to tolerate side effects if the treatment could control disease progression or prevent recurrence. Based on the CBCN survey, close to two-thirds of patients indicated that when it came to fatigue, nausea, depression, problems with concentration, memory loss, diarrhea, and insomnia, some or a moderate impact on one's QoL would be considered acceptable, and approximately one-quarter of patients indicated that a strong or debilitating impact would be considered acceptable for an agent that could prolong progression by six months. Patients noted that they understood the limitations of current treatment options, and sought to live their remaining months and years with the best QoL that they could achieve.

Input was received from 18 patients with experience using palbociclib plus fulvestrant. Among them, 17 indicated having been diagnosed with HR-positive, HER2-negative mBC (one declined to answer). Patients indicated that PFS is a chief concern for them and is expected to be extended with palbociclib-plus-

fulvestrant treatment. All 17 patients from the RBC survey who had experience with palbociclib indicated they would recommend the drug to other patients with mBC. According to RBC, more than half gave the side effects with palbociclib plus fulvestrant a score of less than 5 on a scale of 1 (completely tolerable) to 10 (completely intolerable), with an average score of 4.47. Fatigue (82%) and neutropenia (65%) were the most commonly cited side effects associated with palbociclib. According to CBCN, seven of the eight patients reported side effects that included fatigue, hair thinning, diarrhea, sore mouth, and neutropenia. All patients interviewed indicated that the side effects they experienced were acceptable.

pERC noted that the 6.6 months' improvement in PFS from the October 2015 data cut-off is clinically meaningful for patients. Although AEs with palbociclib plus fulvestrant were increased compared with fulvestrant monotherapy, pERC agreed they could be managed in clinical practice through dose adjustments. Patients' willingness to tolerate moderate to debilitating side effects for improvements in PFS were also acknowledged by pERC. Furthermore, based on clinician input and conclusions by the CGP, pERC agreed that palbociclib plus fulvestrant will be a more tolerable treatment option for patients compared with everolimus plus exemestane.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility and cost-effectiveness

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility and cost-effectiveness analysis for the treatment of patients with HR-positive, HER2-negative, locally aBC or mBC who have progressed on prior endocrine therapy. Palbociclib plus fulvestrant was compared with fulvestrant. An NMA was also conducted to compare palbociclib plus fulvestrant with other AIs or everolimus plus exemestane.

Basis of the economic model: Clinical and economic inputs

Costs considered in the model included drug costs, disease management costs, post-progression management costs, and AE costs. The key clinical effects considered in the model were PFS, OS (from PALOMA-3 and NMA), and utilities (PALOMA-3 and literature). Long-term extrapolation of OS and estimates of utilities had the biggest impact on the incremental cost-effectiveness ratio (ICER).

Drug costs: Generic fulvestrant and everolimus expected

Based on costs used in the submitted model, palbociclib costs $253.90 per unit. At the recommended dose of 125 mg once daily for 21 consecutive days, followed by seven days off treatment, palbociclib costs $253.90 per day and $5,332.16 per 28-day cycle.

Based on costs used in the submitted model, fulvestrant costs $582.90 per unit. At the recommended dose of 500 mg on days 0, 14, 28, and every 28 days thereafter, fulvestrant costs $582.90 per day, $2,331.60 for the first cycle, and $1,165.80 for subsequent cycles. pERC noted that fulvestrant is likely to be available as a generic product soon and it is expected the cost will drop substantially.

Based on costs used in the submitted model, everolimus costs $201.25 per unit. At the recommended dose of 10 mg per day, everolimus costs $201.25 per day and $5,634.87 per 28-day cycle. pERC noted that everolimus is likely to be available as a generic product soon and it is expected the cost will drop substantially.

Based on costs used in the submitted model, exemestane costs $1.33 per unit. At the recommended dose of 25 mg, exemestane costs $1.33 per day and $37.14 per 28-day cycle.

Cost-effectiveness estimates: Need for substantial price reduction

pERC deliberated upon the cost-effectiveness of palbociclib plus fulvestrant and concluded that it is not cost-effective when compared with fulvestrant monotherapy or everolimus plus exemestane in women with HR-positive, HER2-negative aBC or mBC. pERC considered a number of contributing factors that led to a substantial increase in the ICER.

For the comparison with fulvestrant and other AIs, pERC noted that the assumption of long-term PFS and OS benefit had the biggest impact on the ICER. Given the absence of long-term PFS and OS data and a lack of demonstrated OS benefit, the pCODR EGP explored several scenarios for extrapolating long-term PFS and OS. When a scenario where the relative treatment effect beyond the trial period was equal

(retained benefit) was explored, the ICER increased by about $20,000 per quality-adjusted life-year (QALY) ($191,613 per QALY base case). In a scenario where the incremental PFS and OS benefit were cut after the end of the trial period (stop and drop method), the ICER increased by nearly $40,000 per QALY. The EGP also explored the impact of a 100% dose intensity, 10-year time horizon (15 years in base case) and utility values from the literature, all of which had smaller impacts on the ICER. When these factors were combined, the EGP ICER ranged from $224,756 to $294,552 per QALY.

pERC further discussed the cost-effectiveness analysis when compared with everolimus plus exemestane. pERC noted that the results of the NMA, conclusions by the CGP, and input by registered clinicians confirmed the absence of an incremental benefit in PFS or OS between the two combinations. Based on this, pERC agreed with the EGP reanalysis setting the hazard ratio for PFS and OS to 1. This resulted in a $40,000 per QALY increase in the ICER ($122,172 per QALY base case). pERC also acknowledged that a meaningful difference in toxicity profile is expected between the two combination agents in favour of palbociclib plus fulvestrant. Although it was unclear how well this difference may have been captured by the QoL instruments used in the PALOMA-3 trial, pERC noted that the ICER was sensitive to small differences in utility values once the incremental PFS and OS benefit was removed. To control for potential differences in the methodology of collecting utility values (PALOMA-3 and literature values), the EGP explored the use of utility estimates from the literature for both treatment groups. pERC further noted that the ICER was very sensitive to the dose intensity. While the PALOMA-3 trial was used to estimate the dose intensity for palbociclib, 100% dose intensity was used for everolimus. Given the anticipated toxicity with everolimus plus exemestane, it is reasonable that a dose intensity below 100% would be expected. The EGP explored the impact of having the same dose intensity for both treatment groups. This had the largest impact on the ICER—an increase of nearly $60,000/QALY. When these factors were combined, the ICER increased substantially and ranged from $633,600 to $698,289 per QALY. Overall, pERC concluded that palbociclib plus fulvestrant is not cost-effective when compared with fulvestrant or everolimus plus exemestane. pERC agreed that a substantial price reduction would be needed to improve the cost-effectiveness of palbociclib plus fulvestrant.

Following the posting of the pERC Initial Recommendation, feedback was received from the submitter noting that the *CADTH Guidelines for the Economic Evaluation of Health Technologies* stipulate that parameter uncertainty be addressed using a probabilistic sensitivity analysis (PSA). In response to this feedback, the EGP presented the probabilistic reanalyses for the upper and lower bounds of both comparisons (fulvestrant and everolimus plus exemestane). Based on the probabilistic analysis, the ICERs for the comparison with fulvestrant remained relatively consistent with the deterministic results ($64,035 per QALY at the lower and $105,641 per QALY at the upper bound). The probabilistic results, however, showed that palbociclib plus fulvestrant was dominated (more costly and less effective) by everolimus plus exemestane. pERC discussed these results and reiterated that a meaningful difference in toxicity profile is expected between the two combination agents in favour of palbociclib plus fulvestrant, although it was unclear how well this difference may have been captured by the QoL instruments used in the PALOMA-3 trial. pERC acknowledged that the EGP attempted to account for possible differences in how utilities were captured in its reanalysis. Overall, pERC agreed that there is uncertainty in the magnitude of benefit anticipated through this difference in toxicity. Given that small changes in the incremental benefit can have dramatic impacts on the ICER, as is demonstrated through the probabilistic results, pERC agreed that a substantial price reduction would be appropriate to ensure that palbociclib plus fulvestrant is cost-effective. Furthermore, the EGP provided the results of a sequential analysis where all comparators were evaluated. Based on this analysis and the principles of extended dominance (scenario where an ICER relative to the next less costly un-dominated intervention is greater than that of a more costly intervention or provides less benefit that this more costly intervention), everolimus plus exemestane was more cost-effective than palbociclib plus fulvestrant.

Further feedback was received from the manufacturer regarding the EGP's use of an HR equal to one for both PFS and OS on the comparison between everolimus plus exemestane and palbociclib plus fulvestrant. pERC noted responses from the EGP reiterating that there is uncertainty in the clinical effect estimates derived from the NMA for the comparison of interest, uncertainty that would not be captured by the HR and subsequently the PSA. This. This was echoed by the CGP's conclusions. The EGP also discussed that methodology for assessing uncertainty in HRs is more established for instances where the clinical inputs are based on randomized controlled trials and not where there is considerable uncertainty, as with an NMA. Additionally, the methodologies discussed by the submitter's feedback were developed at a time when NMAs were not widely in use. Lastly, although the EGP was able to explore some assumptions regarding the clinical benefit for the main comparison, the model did not allow the alteration of clinical benefits estimated in the NMA.

The EGP also responded to feedback from the submitter related to the source of the utilities data used in the base case results. The submitter commented that utilities for the comparison between palbociclib plus fulvestrant to fulvestrant were derived from the PALOMA-3 trial. The EGP however reiterated that the post-progression utilities for both active treatment and BSC/chemotherapy were derived from the Lloyd formula.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Substantial budget impact
pERC considered the feasibility of implementing a reimbursement recommendation for palbociclib plus fulvestrant and highlighted a number of concerns. pERC noted that there is no evidence to support the use of palbociclib plus fulvestrant in the front-line setting nor for the sequential use of CDK 4/6 inhibitors with a change in the combination hormone. pERC noted that the PALOMA-3 trial included patients who have had one to more than three prior lines of therapy and agreed it would be reasonable to offer palbociclib plus fulvestrant in patients who may have already completed second-line or beyond therapy, including patients who may have progressed on everolimus plus exemestane, an AI, or chemotherapy. pERC also noted a time-limited need to switch patients currently on everolimus plus exemestane, an AI, or chemotherapy to palbociclib plus fulvestrant. pERC noted that the number of patients who are expected to receive palbociclib plus fulvestrant in the second-line setting is small (given that most patients will receive a CDK 4/6 inhibitor plus AI in the first-line setting); however, there is a large prevalent population that may be on everolimus plus exemestane or an AI in the first-line setting and who will be eligible for palbociclib plus fulvestrant upon progression.

pERC also noted that the use of an Ontario perspective to determine the number of patients who will be eligible for public reimbursement of palbociclib plus fulvestrant may not be most representative of Canadian practice, as there is variability in the funding structures for oral agents across jurisdictions. Based on these factors, pERC agreed that the market share of palbociclib plus fulvestrant will be possibly higher than what is depicted in the submitted BIA. Given the prevalent population and the availability of first-line palbociclib, it is difficult to calculate the population for this indication/setting but it is likely to decrease over time. pERC further highlighted that the optimal sequencing of palbociclib plus fulvestrant and other treatments now available for the treatment of patients with locally advanced or mBC who have received prior therapy is currently unknown. Therefore, pERC recognized that provinces would need to address treatment sequencing upon implementation of palbociclib plus fulvestrant, and noted that collaboration among provinces to develop a common approach would be of value.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Maureen Trudeau was excluded from chairing and voting due to a conflict of interest
- Dr. Anil Abraham Joy and Lauren Flay Charbonneau were excluded from voting due to conflicts of interest
- Daryl Bell did not vote due to his role as a patient member alternate.

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Christine Kennedy, who was not present for the meeting
- Dr. Maureen Trudeau was excluded from chairing and voting due to a conflict of interest
- Dr. Anil Abraham Joy and Lauren Flay Charbonneau were excluded from voting due to conflicts of interest
- Daryl Bell did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All pERC members must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of palbociclib plus fulvestrant for hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer or metastatic breast cancer, through their declarations, six members had a real, potential, or perceived conflict; based on the application of the *pCODR Conflict of Interest Guidelines*, three of these members were excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for

informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation

• PAG is seeking information on data comparing palbociclib plus fulvestrant with currently available treatments.
• PAG is seeking guidance on the appropriateness of palbociclib plus fulvestrant for:
  • Male patients with breast cancer
  • Patients who had extensive symptomatic visceral metastasis
  • Patients who had uncontrolled CNS metastases
  • Patients who had an ECOG PS of 2
  • Patients who are HER2 double equivocal (both IHC and ISH/FISH are equivocal)
	• pERC agreed there may be a net clinical benefit compared with everolimus plus exemestane and other single-agent AIs. pERC further agreed that palbociclib plus fulvestrant is likely more effective than tamoxifen.
	• pERC agreed that the PALOMA-3 data can be generalized to male patients with HR+ HER2- breast cancer and patients who have HER2 double equivocal disease (who are considered HER2-negative). pERC further noted that the decision to treat patients with an ECOG PS greater than 1 should be left to the treating oncologist.
	• pERC agreed that the PALOMA-3 data should not be generalized to patients with extensive symptomatic visceral metastases or uncontrolled CNS metastases.

• PAG is seeking clarity on whether patients who had received previous systemic chemotherapy and endocrine therapy would be eligible, as the first-line trials of palbociclib excluded patients who received previous systemic chemotherapy. • PAG is also seeking confirmation that eligibility with respect to timing of disease relapse or progression on endocrine therapy in the adjuvant or advanced setting would align with that in the PALOMA-3 trial.	• pERC noted that the PALOMA-3 trial included patients who had previous chemotherapy and endocrine therapy; therefore, it is reasonable to offer palbociclib plus fulvestrant to these patients, given that they meet all other PALOMA-3 trial inclusion criteria. • pERC agreed that eligibility for palbociclib plus fulvestrant with respect to timing of relapse or progression on endocrine therapy in the adjuvant or advanced setting should follow the PALOMA-3 trial design.
• PAG is seeking confirmation that patients treated with a first-line CDK 4/6 inhibitor (i.e., palbociclib, ribociclib) plus an AI would not be eligible for palbociclib plus fulvestrant. • PAG is seeking guidance on the appropriateness, for patients who received palbociclib plus an AI in the first-line setting and started progressing, of continuing with palbociclib but switching the AI for fulvestrant.	• pERC agreed that there is no good evidence to suggest that patients receiving palbociclib with an AI as first-line treatment, who develop disease progression, would benefit from substituting the AI with fulvestrant and continuing palbociclib. Furthermore, if patients have already received another CDK 4 or 6 inhibitor, such as ribociclib, they would not be appropriate candidates for treatment with palbociclib plus fulvestrant.

• PAG noted the following groups of patients would need to be addressed on a time-limited basis:
  • Patients who recently started on single-agent fulvestrant.
  • Patients who recently started chemotherapy for relapsed disease.
  • Patients already treated or currently treated with everolimus plus exemestane.
  • Patients who have progressed on or are currently on second-line endocrine therapy.
	• pERC agreed that there is a time-limited need to switch patients who are currently on single-agent fulvestrant (recognizing that patients would not be accessing fulvestrant monotherapy through provincial funding), patients who recently started chemotherapy for relapsed disease, patients currently on everolimus plus exemestane.
	• Furthermore, pERC agreed that there is a time-limited need to treat patients who recently progressed on the above-mentioned therapies with palbociclib plus fulvestrant as long as they have not been treated with a CDK 4/6 inhibitor in another setting.

• PAG is seeking guidance on the appropriate sequencing of all available treatments for HR-positive, HER2-negative advanced breast cancer for patients who receive palbociclib plus fulvestrant and then develop metastatic disease.	• pERC concluded that the optimal sequencing of palbociclib plus fulvestrant and other therapies now available for the treatment of patients with metastatic breast cancer is currently unknown. Therefore, pERC was unable to make an evidence-

• What treatments can they receive following palbociclib plus fulvestrant? • How should everolimus plus exemestane be sequenced? As previously mentioned, this combination is not funded after palbociclib plus letrozole in the first-line setting.	informed recommendation on the sequencing of treatment. pERC noted that jurisdictions may want to consider developing a common approach to treatment sequencing of all available drugs in this setting.
• PAG is also seeking guidance on the interchangeability of CDK 4/6 inhibitors (i.e., palbociclib, ribociclib) in this setting.	• pERC agreed that there is no evidence to support the interchangeability of CDK 4/6 inhibitors in this setting.

AI = aromatase inhibitor; CDK = cyclin-dependent kinase; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; IHC = immunohistochemistry; ISH/FISH = in situ hybridization/fluorescence in situ hybridization; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; PS = Performance Status.