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: Abemaciclib (VERZENIO)
Reimbursement Request:
For the treatment of hormone receptor -positive (HR+), human epidermal growth factor receptor 2 -negative (HER2-) advanced or metastatic breast cancer:

- In combination with an aromatase inhibitor in postmenopausal women as initial endocrine-based therapy. (First-Line Systemic Therapy/Endocrine Sensitive)
- In combination with fulvestrant in women with disease progression following endocrine therapy (Endocrine-Resistant). Pre- or perimenopausal women must also be treated with a gonadotropin-releasing hormone agonist

Submitted By: Eli Lilly Canada Inc.	Manufactured By: Eli Lilly Canada Inc.
NOC Date: April 5, 2019	Submission Date: December 3, 2018
Initial Recommendation: May 3, 2019	Final Recommendation: July 5, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Cost of abemaciclib plus letrozole	• $1.19 per mg • $96.58 per day • $5,408.37 per 28-day course
	Cost of abemaciclib plus anastrozole	• $1.91 per mg • $96.47 per day • $5,402.48 per 28-day course
	Cost of abemaciclib plus fulvestrant	• $2.97 per mg • $232.04 per day • $6,497.00 per 28-day course for cycle 2 onwards • Cost for cycle 1 (including fulvestrant loading dose) = $7,662.80

pERC RECOMMENDATION

☐ Reimburse

☒ Reimburse with clinical criteria and/or conditions*

☐ Do not reimburse

* If the condition(s)

pERC issued separate recommendations for first-line systemic therapy /endocrine sensitive patients and for endocrine-resistant patients in the advanced or metastatic setting.

First-Line Systemic Therapy/Endocrine Sensitive *(first-line systemic therapy or endocrine sensitive in the advanced or metastatic setting and at least 12 months since completing adjuvant hormonal therapy)*

pERC conditionally recommends the reimbursement of abemaciclib in combination with non-steroidal aromatase inhibitor (NSAI)for the treatment of HR+, HER2- advanced or metastatic breast cancer in patients as initial endocrine-based therapy (i.e., who have not received any prior

cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.	treatment for advanced or metastatic disease) if the following condition is met: • Cost-effectiveness being improved to an acceptable level. • The public drug plan cost of abemaciclib should not exceed the public drug plan cost of other available cyclin-dependent kinase (CDK) 4/6 inhibitors. Eligible patients include men and postmenopausal women with good performance status who are unable to tolerate or have a contraindication to available CDK 4/6 inhibitors. Women rendered postmenopausal (either chemically or surgically) are eligible (i.e., premenopausal or perimenopausal women must also be treated with a gonadotropin-releasing hormone agonist or bilateral salpingo-oophorectomy). Treatment should be continued until disease progression or unacceptable toxicity. pERC made this recommendation because it was satisfied that there is a net clinical benefit of abemaciclib plus NSAI compared with a NSAI alone based on a statistically significant and clinically meaningful prolonged progression-free survival (PFS) and a manageable, but not an insignificant, toxicity profile. However, pERC's assessment of net clinical benefit was tempered by the lack of evidence, at this time, demonstrating a clinically meaningful and statistically significant improvement in overall survival (OS), and the clinically meaningful difference in diarrhea symptom score favouring NSAI alone, despite the similar global health status score. pERC concluded that abemaciclib plus NSAI aligns with the following patient values: delaying disease progression and providing an additional treatment choice with manageable, but not insignificant, side effects. pERC concluded that, at the submitted price, abemaciclib plus NSAI is not cost-effective compared with NSAI alone. In addition, pERC also concluded that, at the submitted price, abemaciclib plus NSAI cannot be considered cost-effective compared with palbociclib plus NSAI or ribociclib plus NSAI due to the uncertainty in the indirect comparison between abemaciclib plus NSAI and these agents. **Endocrine-Resistant *(progressive disease after prior endocrine therapy in the metastatic setting)*** pERC conditionally recommends the reimbursement of abemaciclib for the treatment of HR+, HER2- advanced or metastatic breast cancer, in combination with fulvestrant in patients with disease progression following endocrine therapy if the following condition is met: • Cost-effectiveness being improved to an acceptable level. Eligible patients include patients with disease progression following endocrine therapy with a good performance status. Premenopausal or perimenopausal women must also be treated with a gonadotropin-releasing hormone agonist. Treatment should be continued until disease progression or unacceptable toxicity. pERC made this recommendation because it was satisfied that compared with fulvestrant alone, there is a net clinical benefit of abemaciclib plus fulvestrant based on a statistically significant and clinically meaningful prolonged PFS, and a manageable, but not insignificant toxicity profile. However, pERC's assessment of net clinical benefit was tempered by the lack of evidence, at this time, demonstrating a statistically significant improvement in OS, and the clinically meaningful difference in diarrhea symptom score favouring fulvestrant alone.

	pERC concluded that abemaciclib plus fulvestrant aligns with the following patient values: delaying disease progression and providing an additional treatment choice with manageable, but not insignificant, side effects. pERC concluded that, at the submitted price, abemaciclib plus fulvestrant is not cost-effective compared with fulvestrant alone. In addition, pERC also concluded that, at the submitted price, abemaciclib plus fulvestrant cannot be considered cost-effective compared with exemestane plus everolimus or palbociclib plus fulvestrant, due to the uncertainty in the indirect comparison between abemaciclib plus fulvestrant and these agents.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

First-Line Systemic Therapy/ Endocrine Sensitive

Pricing Arrangements to Improve Cost- Effectiveness and Budget Impact
Given that pERC concluded that there is a net clinical benefit with abemaciclib plus NSAI in the first-line systemic therapy/endocrine sensitive population described above, jurisdictions will need to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and affordability of abemaciclib plus NSAI. The public drug plan cost of abemaciclib should not exceed the public drug plan cost of other available cyclin-dependent kinase (CDK) 4/6 inhibitors.

Need for Appropriate Monitoring Due to Toxicity Concerns with Abemaciclib plus NSAI
Given the risks of toxicity with abemaciclib plus NSAI, pERC noted that jurisdictions should consider developing guidelines or processes to monitor and manage toxicity in patients who receive abemaciclib.

Revised Network Meta-Analysis and Economic Model for Consideration of Reimbursement for All Patients in First-Line Setting
pERC concluded that abemaciclib plus NSAI should only be considered for patients who are unable to tolerate or have a contraindication to available CDK 4/6 inhibitors because limitations of the submitted network meta-analysis (NMA) comparing abemaciclib plus NSAI to palbociclib plus NSAI and ribociclib plus NSAI limited pERC's confidence in the outcomes. pERC noted that a resubmission could potentially be considered for the reimbursement of abemaciclib plus NSAI in the first-line setting (regardless of intolerance to available CDK 4/6 inhibitor) if:

- a revised NMA addressed the following limitations: heterogeneity, immature OS data, and exclusion of QoL and safety outcomes related to diarrhea
- a revised economic model that addressed the limitations of the NMA, used abemaciclib plus NSAI as the reference case in the NMA, and used data from a single source (i.e., NMA) as opposed to multiple sources (NMA and MONARCH 3) to obtain the comparative efficacy.

Abemaciclib in Combination with Aromatase Inhibitor
In acknowledging consistency with the funded CDK 4/6 inhibitor, pERC noted that it would be acceptable to reimburse abemaciclib with any aromatase inhibitor (AI), instead of limiting to letrozole and anastrozole. Therefore, at the time of implementing a reimbursement recommendation for abemaciclib plus NSAI, jurisdictions may consider extending the reimbursement to abemaciclib in combination with any aromatase inhibitor.

Endocrine resistant

Pricing Arrangements to Improve Cost- Effectiveness and Budget Impact
Given that pERC concluded that there is a net clinical benefit with abemaciclib plus fulvestrant in the endocrine-resistant population described above, jurisdictions will need to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and affordability of abemaciclib plus fulvestrant.

Need for Appropriate Monitoring Due to Toxicity Concerns with Abemaciclib plus Fulvestrant
Given the risks of toxicity with abemaciclib plus fulvestrant, pERC noted that jurisdictions should consider developing guidelines or processes to monitor and manage toxicity in patients who receive abemaciclib.

Availability of Other CDK 4/6 inhibitors
pERC recognized that another CDK 4/6 inhibitor with fulvestrant may become a funded treatment option in the future and indicated that there may be a preference to use other available CDK 4/6 inhibitors with more favourable

toxicity profiles and administration schedules. pERC noted the statistically significant worsening and clinically meaningful difference in diarrhea symptom score reported for abemaciclib, which was not reported in the pCODR reviews for other CDK 4/6 inhibitors.

Time Limited Need for Patients who have recently Started Treatment with Fulvestrant

At the time of implementing a reimbursement recommendation for abemaciclib plus fulvestrant, jurisdictions may consider addressing the time-limited need of adding abemaciclib to patients who recently initiated treatment with fulvestrant. pERC noted that this approach would be appropriate, given that patients have been able to receive compassionate supply fulvestrant.

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

First-Line Systemic Therapy/Endocrine Sensitive

Breast cancer is the most common diagnosed malignancy in Canadian women, with an estimated 26,300 new cases and 5,000 deaths in 2017. While many women diagnosed with early stage breast cancer will be cured with treatment, some women will experience a relapse of their breast cancer (metastatic spread to other organs), with an additional 5% to 10% of women who will present with de novo metastatic breast cancer. Advanced or metastatic breast cancer remains incurable and is treated systematically with palliative intent. In the setting of metastatic disease, median life expectancy is approximately two to three years. pERC acknowledged that treatment options are available in the first-line setting, including another CDK 4/6 inhibitor. pERC recognized that intolerance (i.e., unmanageable toxicity) to CDK 4/6 inhibitors may occur. Therefore, pERC concluded that there is a need for abemaciclib plus NSAI in patients who are unable to tolerate or have contraindications to other available CDK 4/6 inhibitors. pERC noted that intolerance to other available CDK 4/6 inhibitors should be based on a mutual assessment by the treating physician and patient. Upon reconsideration, pERC discussed the submitter's feedback that the recommendation limits clinical judgment and noted that the Canadian Breast Cancer Network shared similar concerns regarding patient choice. pERC maintained that the recommendation offered clinicians an alternative option for treating first-line systemic therapy for advanced or metastatic breast cancer and disagreed that the recommendation limited patient choice. pERC discussed that abemaciclib is not a novel CDK 4/6 inhibitor and reiterated that treatment options are available in the first-line setting, including another CDK 4/6 inhibitor. pERC affirmed that drugs are assessed based on relevant comparators, which include currently recommended and/or available drugs in the same class at the time of review and as a result, pERC concluded that abemaciclib should not be seen as the first/novel CDK 4/6 inhibitor and reiterated that abemaciclib fulfills a need in patients who are unable to tolerate or have contraindications to other available CDK 4/6 inhibitors.

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 a phase III, multi-centre, randomized, double-blind, placebo-controlled study (MONARCH 3) of abemaciclib plus NSAI or placebo plus NSAI (NSAI alone) in postmenopausal women with HR+, HER2− advanced or metastatic breast cancer who had not received any previous systemic therapy in the advanced/metastatic setting. pERC discussed that there was a statistically significant and clinically meaningful improvement in PFS for patients receiving abemaciclib plus NSAI compared with NSAI alone in the MONARCH 3 trial. pERC acknowledged that the OS data were immature; and as a result, there was the lack of evidence to demonstrate a statistically significant improvement in OS for patients receiving abemaciclib plus NSAI compared with NSAI alone. Upon reconsideration, pERC discussed the submitter's feedback and disagreed that abemaciclib was held to a higher standard for OS compared with ribociclib. pERC reiterated that drugs are assessed based on relevant comparators, which include currently recommended and/or available drugs in the same class at the time of review. Notwithstanding that ribociclib also did not have mature OS data, pERC agreed that at this time, there was a lack of statistically significant and clinically meaningful improvement in OS demonstrated by abemaciclib plus NSAI.

pERC discussed that the QoL measured in the MONARCH 3 trial found a statistically significant worsening and clinically meaningful difference in diarrhea symptom score experienced by the patients in the abemaciclib plus NSAI group compared with patients in the NSAI alone group. pERC also noted a statistically significant (but not clinically meaningful differences) worsening for other symptom scores such as nausea and vomiting, appetite loss, and fatigue; and functioning scores such as global health status, role functioning and social functioning. pERC recognized that the health related QoL data were not from peer-reviewed publications and were only available through a poster. Moreover, pERC acknowledged that these data were limited to the comparison of abemaciclib plus NSAI and NSAI alone; no data comparing abemaciclib plus NSAI to other CDK 4/6 inhibitors were available. pERC did however acknowledge that clinically meaningful scores in diarrhea were not reported in the pCODR reviews for other CDK 4/6 inhibitors.

In terms of safety, pERC discussed that diarrhea was the most common adverse event (AE) experienced by women receiving abemaciclib plus NSAI. pERC noted that the onset of diarrhea was early and that most patients experienced grade 1 or 2 diarrhea, which pERC felt was likely manageable in most cases. As well, pERC noted that discontinuation due to diarrhea for the abemaciclib plus NSAI group was low (2%) however, pERC acknowledged that 25% of patients in the abemaciclib plus NSAI group discontinued treatment due to an AE compared with 4% of the NSAI group. Furthermore, pERC noted that 47% of patients in the abemaciclib plus NSAI group had a dose reduction due to AEs compared with about 6% of patients in the NSAI alone group. Overall, pERC concluded that compared with NSAI alone, abemaciclib plus NSAI had manageable, but not insignificant, toxicity. However, pERC reiterated that these toxicities and QoL results experienced by patients treated with abemaciclib plus NSAI were not insignificant. Ultimately, this led pERC to conclude that despite the availability of other treatment options in the first-line setting (including another CDK 4/6 inhibitor), there is a need for abemaciclib plus NSAI in patients who are unable to tolerate or have contraindications to other available CDK 4/6 inhibitors. Upon reconsideration, pERC discussed the feedback from the submitter and respectfully disagreed with the submitter that the recommendation placed undue emphasis on diarrhea and created an inaccurate impression that abemaciclib has a worse safety profile than other CDK 4/6 inhibitors. pERC discussed that drugs are assessed based on relevant comparators, which include currently recommended and/or available drugs in the same class at the time of review. pERC acknowledged differences in the safety profile among the CDK 4/6 inhibitors noted by the Clinical Guidance Panel and registered clinicians (upon feedback) (e.g., with less neutropenia and more diarrhea with abemaciclib, less hepatotoxicity and more neutropenia with palbociclib, and potential for QT interval prolongation with ribociclib). pERC reiterated that diarrhea is a significant toxicity for patients and that there was a clinically meaningful difference in diarrhea favouring the NSAI alone group when compared with abemaciclib plus NSAI group. Despite the similar Global Health status score, pERC felt it was important not to overlook the clinically meaningful difference in diarrhea symptom score favouring NSAI alone.

Upon reconsideration, pERC noted that the submitter referenced a pooled post-hoc subgroup analysis (suggesting the benefit of abemaciclib was evident, even in poor prognostic patients). pERC acknowledged that the Methods team confirmed that this reference was captured in the literature search; however, it was excluded in the initial screening phase because it was a pooled analysis of data from MONARCH 2 and MONARCH 3 trials, which used different inclusion criteria and abemaciclib combinations. pERC agreed with the Methods team's rationale for excluding the pooled post-hoc subgroup analysis from the systematic review.

In addition to the MONARCH 3 trial, pERC also deliberated upon an NMA that compared many treatments including abemaciclib plus NSAI, palbociclib+ NSAI and ribociclib plus NSAI. The NMA considered efficacy outcomes (e.g., PFS, OS), but it did not adequately consider QoL or safety because of the limited data available for these outcomes. pERC noted that QoL and safety are relevant and important outcomes in this patient population due to the considerable toxicity associated with abemaciclib, especially with respect to diarrhea, compared with other available CDK 4/6 inhibitors. While abemaciclib plus NSAI was considered similar to palbociclib plus NSAI and ribociclib plus NSAI for PFS, overall response rate, and clinical benefit rate, no conclusions could be drawn on OS due to the immaturity of the OS data included in the NMA. Finally, pERC also noted the substantial heterogeneity of the patient population included in the NMA in terms of important characteristics such as HR+, HER2- status, disease-free interval, site of disease, prior chemotherapy, prior endocrine therapy, and visceral involvement at baseline, which also limited confidence in the outcomes of the NMA. pERC noted that no subgroup analyses were conducted to address the heterogeneity, while acknowledging a meta-regression analysis was not considered due to limited study data available. Nonetheless, pERC felt that conducting subgroup analyses to address the heterogeneity could have helped reduce the uncertainty in the NMA. Although pERC concluded that there was a net clinical benefit of abemaciclib plus NSAI compared with NSAI alone based on the results of the MONARCH 3 trial, when the submitted NMA results were reviewed, pERC concluded that the uncertainty of a net clinical benefit of abemaciclib plus NSAI compared with other available CDK 4/6 inhibitors remains. Upon reconsideration, pERC disagreed with the submitter's feedback that the NMA for the abemaciclib submission was held to a higher standard than the NMA for previous pCODR reviews for similar patient populations. pERC reiterated their concerns related to toxicity profile of abemaciclib and the statistically significant worsening and clinically meaningful difference in diarrhea symptom score experienced by the abemaciclib group. pERC noted that in previous pCODR reviews for similar patient populations, safety outcomes were included in the NMA. pERC reiterated that the inclusion of QoL and safety outcomes related to diarrhea as an outcome in the abemaciclib NMA may have reduced pERC's concerns related to diarrhea and quality of life.

pERC discussed the registered clinician input and agreed with the clinicians that abemaciclib plus NSAI could serve as another option particularly in the setting of intolerance to first-line palbociclib plus NSAI. Moreover, pERC discussed that some of the registered clinicians indicated that palbociclib would be the preferred option compared with abemaciclib because of the once daily dosing, fewer drug interactions, less need for cardiac monitoring, and the low rate of diarrhea associated with palbociclib. Upon reconsideration, pERC discussed the registered clinicians' preference for a more consistent recommendations across the class of CDK 4/6 inhibitors and acknowledged that different eligibility criteria may make it confusing for clinicians and patients. As noted by the registered clinicians, palbociclib is currently funded in Ontario for use with any of letrozole, anastrozole or exemestane. In acknowledging consistency with the funded CDK 4/6 inhibitor, pERC agreed with the registered clinicians that it would be acceptable to extend funding to use of abemaciclib with any AI, instead of limiting to letrozole and anastrozole. As well, upon reconsideration, pERC acknowledged the registered clinicians' request to clarify that eligible patients include pre- and peri-menopausal patients that are treated with a gonadotropin-releasing hormone (GnRH) agonist (for the first-line systemic therapy/endocrine sensitive setting) and agreed to include this specification in the recommendations for clarity and consistency with the endocrine-resistant recommendation.

pERC deliberated on the input from two patient advocacy groups and concluded that abemaciclib plus NSAI aligns with the following patients' values: delaying disease progression and providing an additional treatment choice with a manageable toxicity profile. pERC noted that improved survival was valued by patients, however, given that OS data were immature in the MONARCH 3 trial, it is unclear if there is a statistically significant improvement in OS. Finally, pERC discussed that abemaciclib plus NSAI would offer patients an additional treatment choice, especially for patients who are intolerant to other available CDK 4/6 inhibitors. Upon reconsideration, pERC discussed Rethink Breast Cancer's request to clarify the eligibility of treatment-naive patients and acknowledged that from a patient perspective, intolerance, or contraindication to a CDK 4/6 inhibitor may not appear to be treatment naive. As a result, pERC revised the recommendation wording to a specific first-line systemic therapy as opposed to treatment naive.

pERC also deliberated on the cost-effectiveness of abemaciclib plus NSAI compared with NSAI alone, palbociclib plus NSAI, and ribociclib plus NSAI. With respect to abemaciclib plus NSAI compared with NSAI alone, pERC noted the Economic Guidance Panel (EGP)'s lower and upper estimates and acknowledged that the EGP's upper estimate was notably higher than in other pCODR reviews for breast cancer drugs in the first-line setting. pERC understood the EGP's rationale for shortening the time horizon to the trial follow-up period for their upper limit; however, pERC disagreed with this approach and felt that it was an extreme measure to address uncertainty in the economic model. As well, pERC noted that in the EGP's lower estimate reanalysis, abemaciclib plus NSAI produced less quality-adjusted life-years (QALY) than NSAI alone (for the progression-free and post-progression states). pERC interpreted this as a potential harm in QALYs associated with abemaciclib which they considered to be a reflection of the amount of uncertainty in the economic analysis, but also a possible reflection of the clinically meaningful and statistically significant difference in diarrhea. Finally, pERC noted that the EGP's best-case estimate was based on the relative efficacy of the MONARCH 3 trial and a 15-year time horizon and concluded that abemaciclib plus NSAI compared with NSAI alone was not cost-effective.

pERC noted that the submitter selected anastrozole/letrozole as the reference case for the NMA used in the economic model, rather than their abemaciclib plus NSAI. As a result, pairwise estimates of relative effect between the abemaciclib plus NSAI and comparators of interest (e.g., palbociclib plus NSAI or ribociclib plus NSAI) were not used in the economic model. Nonetheless, pERC acknowledged that regardless of the reference case from the NMA used in the economic model, there still remained uncertainty in comparative effectiveness of palbociclib plus NSAI, and ribociclib plus NSAI compared with abemaciclib plus NSAI due to the heterogeneity in the NMA. Moreover, pERC noted that multiple sources (NMA and MONARCH 3) were used in the economic model to obtain the comparative efficacy; for instance, time to progression for the abemaciclib plus NSAI and NSAI was taken from the MONARCH 3 trial and for the comparators, hazard ratios were derived from the NMA. pERC felt that it was more appropriate to use a single source (i.e., NMA) as opposed to multiple sources (NMA and MONARCH 3) to obtain the comparative efficacy. As a result, pERC concluded that the results of the cost-effectiveness of abemaciclib plus NSAI compared with palbociclib plus NSAI, and ribociclib plus NSAI need to be interpreted with caution. pERC did acknowledge the EGP's extensive reanalyses comparing abemaciclib plus NSAI with palbociclib plus NSAI or ribociclib plus NSAI to address the limitations of the NMA and agreed with the EGP's focus on abemaciclib plus NSAI compared with NSAI alone. Lastly, pERC felt that a revised economic model adequately addressing the limitations of the NMA (e.g., conduct subgroup analyses to address heterogeneity, inclusion of mature OS data, and inclusion of QoL and safety outcomes

related to diarrhea), using abemaciclib plus NSAI as the reference case (as opposed to NSAI alone) in the NMA, and using a single source (i.e., NMA) to obtain comparative efficacy could reduce the uncertainty in the cost-effectiveness and provide better clarity on how abemaciclib plus NSAI compares with other available initial endocrine-based therapies. pERC noted that a resubmission could potentially be considered for the reimbursement of abemaciclib plus NSAI in the first-line setting (regardless of intolerance to available CDK 4/6 inhibitors) if the above considerations were fulfilled.

pERC considered the feasibility of implementing a reimbursement recommendation for abemaciclib plus NSAI for first-line systemic therapy in patients with endocrine-sensitive disease. pERC noted that the factors that most influence the budget impact analysis include: the number of treatment cycles, the ratio of used and planned dose intensity, and the variation in the uptake rate of abemaciclib plus NSAI. For instance, pERC noted that the budget impact analysis (BIA) assumed market share was taken from CDK 4/6 inhibitor competitors, however, if market share was taken from NSAI, then the BIA was increased significantly. Although the MONARCH 3 trial only included patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 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 abemaciclib plus NSAI. Furthermore, pERC concluded that it would be reasonable to include male patients with HR+, HER2- advanced or metastatic breast cancer in the eligible patient population. In addition, pERC noted the twice daily administration schedule compared with the once daily administration of other CDK 4/6 inhibitors was a barrier to implementation and how the twice daily dosing schedule could affect patients' compliance with therapy.

Lastly, pERC deliberated on the input from PAG, in particular on the factors related to currently funded treatments, the eligible population, implementation factors and sequencing and priority of treatments. Refer to the summary table in Appendix 1 for more details.

Endocrine resistant

pERC acknowledged that there is an available, funded treatment for patients with disease progression following endocrine therapy (exemestane plus everolimus) and noted that pERC recently made a recommendation for a CDK 4/6 inhibitor (palbociclib plus fulvestrant) in a similar indication that is not currently publicly funded. Therefore, pERC recognized that there is a need for abemaciclib plus fulvestrant in patients with HR+, HER2- advanced or metastatic breast cancer whose disease had progressed on previous endocrine therapy.

pERC deliberated upon the results of a phase III, multi-centre, randomized, double-blind, placebo-controlled study (MONARCH 2) of abemaciclib plus fulvestrant or placebo plus fulvestrant (fulvestrant alone) in women with HR+, HER2– advanced or metastatic breast cancer whose disease had progressed on previous endocrine therapy. pERC discussed that there was a statistically significant and clinically meaningful improvement in PFS for patients receiving abemaciclib plus fulvestrant compared with fulvestrant alone in the MONARCH 2 trial. pERC acknowledged that the OS data were immature; and as a result, there was the lack of evidence to demonstrate a statistically significant improvement in OS for patients receiving abemaciclib plus fulvestrant compared with fulvestrant alone.

pERC discussed that QoL measured in the MONARCH 2 trial found a statistically significant worsening and clinically meaningful difference in diarrhea symptom score experienced by the patients in the abemaciclib plus fulvestrant group compared with patients in the fulvestrant alone group. pERC also noted statistically significant worsening (but not clinically meaningful differences) for other symptom scores such as nausea and vomiting, appetite loss, and systemic therapy side effects (such as dry mouth, eye symptoms, hair loss, and hot flashes). pERC recognized that the health related QoL data were not from peer-reviewed publications and only available through a poster. Moreover, pERC acknowledged that these data were limited to the comparison of abemaciclib plus fulvestrant and fulvestrant alone; no data comparing abemaciclib plus fulvestrant to other relevant treatments were available. pERC did however acknowledge that clinically meaningful scores in diarrhea were not reported in the pCODR review for a similar indication.

In terms of safety, pERC discussed that diarrhea was the most common AE experienced by women receiving abemaciclib plus fulvestrant. pERC also noted that the onset of diarrhea was early, and most patients experienced grade 1 or 2 diarrhea, which pERC felt was likely manageable in most cases. Furthermore, pERC discussed that the most frequent grade 3 or higher AE with the abemaciclib plus fulvestrant was neutropenia (27% versus 2%). As well, pERC discussed that the withdrawal rate due to AEs in the abemaciclib plus fulvestrant group was higher than in the fulvestrant group (16% versus 3%). Furthermore, pERC noted that many more patients in the abemaciclib plus fulvestrant group had a dose reduction due to AEs than patients in the fulvestrant group (43% versus 1%). Overall, pERC concluded that compared with fulvestrant alone, abemaciclib plus fulvestrant had manageable, but not insignificant toxicity. However, pERC reiterated that these toxicities and QoL results experienced by patients treated with abemaciclib plus fulvestrant were not insignificant. Ultimately, with no currently available CDK 4/6 inhibitor option in this setting, pERC acknowledged that there is a need for abemaciclib plus fulvestrant in patients with HR+, HER2- advanced or metastatic breast cancer whose disease had progressed on previous endocrine therapy.

In addition to the MONARCH 2 trial, pERC also deliberated upon an NMA that compared many treatments including abemaciclib plus fulvestrant, palbociclib plus fulvestrant, and exemestane plus everolimus. The NMA considered efficacy outcomes (e.g., PFS and OS), but it did not adequately consider QoL or safety because of the limited data available for these outcomes. pERC noted that QoL and safety are relevant and important outcomes in this patient population due to the potentially increased toxicity associated with abemaciclib, especially with respect to diarrhea, compared with other available treatments. While abemaciclib plus fulvestrant was considered similar to palbociclib plus fulvestrant and exemestane plus everolimus for PFS, overall response rate, and clinical benefit rate, no conclusions could be drawn on OS due to the immaturity of the OS data included in the NMA. Finally, pERC also noted the substantial heterogeneity of the patient population included in the NMA in terms of important characteristics such as HR+, HER2- status, prior chemotherapy, and prior endocrine therapy, which also limited confidence in the outcomes of the NMA. pERC noted that some subgroup analyses were conducted to address the heterogeneity, while acknowledging a meta-regression analysis was not considered due to limited study data available. Although pERC concluded that there was a net clinical benefit of abemaciclib plus fulvestrant compared with fulvestrant alone based on the results of the MONARCH 2 trial, when the submitted NMA results were reviewed, pERC concluded that the uncertainty of a net clinical benefit of abemaciclib plus fulvestrant compared with other available treatments remains.

pERC discussed the registered clinician input and agreed with the clinicians that abemaciclib plus fulvestrant is an option for patients with metastatic HR+, HER2- metastatic breast cancer who have progressed on previous endocrine therapy. pERC recognized that palbociclib plus fulvestrant may become a funded treatment option in the near future and indicated that there may be a preference to use other available CDK 4/6 inhibitors (e.g., palbociclib plus fulvestrant) over abemaciclib given the dosing schedule (once daily versus twice daily). pERC also noted the statistically significant worsening and clinically meaningful difference in diarrhea symptom score reported for abemaciclib, which was not reported in the pCODR reviews for other CDK 4/6 inhibitors.

pERC deliberated on the input from two patient advocacy groups and concluded that abemaciclib plus fulvestrant aligns with the following patients' values: delaying disease progression and providing an additional treatment choice with a manageable toxicity profile. pERC noted that improved survival was valued by patients; however, given that OS data were immature in the MONARCH 2 trial, it was unclear if there is a statistically significant improvement in OS. Finally, pERC discussed that abemaciclib plus fulvestrant would offer patients an additional treatment choice.

pERC also deliberated on the cost-effectiveness of abemaciclib plus fulvestrant compared with fulvestrant alone, palbociclib plus fulvestrant, and exemestane plus everolimus. With respect to abemaciclib plus fulvestrant compared with fulvestrant alone, pERC noted the EGP's lower and upper estimates and acknowledged that the EGP's upper estimate was notably higher than in other pCODR reviews for drugs in similar indications. pERC understood the EGP's rationale for shortening the time horizon to the trial follow-up period for their upper limit; however, pERC disagreed with this approach and felt that it was an extreme measure to address uncertainty in the economic model. As well, pERC noted that in the EGP's lower and upper estimate reanalyses, abemaciclib plus fulvestrant produced less QALY than fulvestrant alone (for the post-progression state). pERC interpreted this as a potential harm in QALYs associated with abemaciclib which they considered to be a reflection of the amount of uncertainty in the economic analysis. pERC noted that the EGP's best-case estimate was based on the relative efficacy of the MONARCH 2 trial and a five-year time horizon and concluded that abemaciclib plus fulvestrant compared with fulvestrant alone was not cost-effective.

pERC noted that the submitter selected fulvestrant as the reference case for the NMA used in the economic model, rather than their abemaciclib plus fulvestrant. As a result, pairwise estimates of relative effect between the abemaciclib plus fulvestrant and comparators of interest (e.g., palbociclib plus fulvestrant or exemestane plus everolimus) were not used in the economic model. Nonetheless, pERC acknowledged that regardless of the reference case from the NMA used in the economic model, there still remained uncertainty in comparative effectiveness of palbociclib plus fulvestrant and exemestane plus everolimus compared with abemaciclib plus fulvestrant due to the heterogeneity in the NMA. Moreover, pERC noted that multiple sources (NMA and MONARCH 2) were used in the economic model to obtain the comparative efficacy; for instance, the submitter obtained the comparative efficacy of abemaciclib plus fulvestrant from the MONARCH 2 trial but obtained the relative treatment effect of exemestane plus everolimus, palbociclib plus fulvestrant, and fulvestrant from the NMA. By using different data sources to inform treatment effect, the submitter assumed that the characteristics of patients enrolled in the MONARCH 2 trial and in other randomized controlled trials (RCTs) included in the indirect comparison report were comparable and did not have any impact on the cost-effectiveness findings. pERC felt that it was more appropriate to use a single source (i.e., NMA) as opposed to multiple sources (NMA and MONARCH 2) to obtain the comparative efficacy. As a result, pERC concluded that the results of the cost-effectiveness of abemaciclib plus fulvestrant compared with palbociclib plus fulvestrant or to exemestane plus everolimus need to be interpreted with caution. pERC did acknowledge the EGP's extensive reanalyses comparing abemaciclib plus fulvestrant with palbociclib plus fulvestrant and exemestane plus everolimus to address the limitations of the NMA and agreed with the EGP's focus on abemaciclib plus fulvestrant compared with fulvestrant alone. Lastly, pERC felt that a revised economic model addressing the limitations of the NMA and using a single source (i.e., NMA) could reduce the uncertainty in the cost-effectiveness and provide better clarity on how abemaciclib plus fulvestrant compares with other available endocrine-based therapies.

pERC considered the feasibility of implementing a reimbursement recommendation for abemaciclib plus fulvestrant for endocrine-resistant patients. pERC noted that the factors that most influence the BIA include the number of treatment cycles, the ratio of used and planned dose intensity, and the variation in the uptake rate of abemaciclib plus fulvestrant. For instance, pERC noted that the BIA assumed market share was taken from CDK4/6 inhibitor competitors not currently funded, however, if market share would

be taken from other endocrine therapies, then the BIA would increase significantly. Although the MONARCH 2 trial only included patients with an ECOG PS of 0 or 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 abemaciclib plus fulvestrant. Furthermore, pERC agreed that it would be reasonable to treat the rare male patients with HR+ HER2- advanced or metastatic breast cancer. In addition, pERC noted that when other CDK 4/6 inhibitors become available, jurisdictions may consider that the public drug plan cost of abemaciclib should not exceed the public drug plan cost of other available cyclin-dependent kinase (CDK) 4/6 inhibitors.

Lastly, pERC deliberated on the input from PAG, in particular on the factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

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 BIA.
- Guidance from the pCODR clinical and economic review panels.
- Input from two patient advocacy groups: Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer.
- Input from two registered clinician input submissions were provided, representing a total of five clinicians. One joint input submission on behalf of four clinicians (three medical oncologists and one oncology pharmacist) from Cancer Care Ontario as well as an individual input by a single medical oncologist.
- Input from pCODR's PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- Two patient advocacy groups, CBCN and Rethink Breast Cancer
- One clinician group: four clinicians (three medical oncologists and one oncology pharmacist) from Cancer Care Ontario
- The PAG
- The submitter (Eli Lilly)

The pERC Initial Recommendation was to reimburse abemaciclib in combination with a nonsteroidal aromatase inhibitor (NSAI) (i.e., anastrozole or letrozole) for the treatment of HR+, HER2- advanced or metastatic breast cancer in patients as initial endocrine-based therapy if the following condition is met: cost-effectiveness being improved to an acceptable level. The pERC initial recommendation was to reimburse abemaciclib for the treatment of HR+, HER2- advanced or metastatic breast cancer, in combination with fulvestrant in patients with disease progression following endocrine therapy if the following condition is met: cost-effectiveness being improved to an acceptable level. PAG agreed with the recommendations and supported early conversion; PAG requested clarification on the reimbursement request criteria and eligible patient population for both recommendations. The submitter agreed in part and did not support early conversion; the submitter disagreed with the abemaciclib in combination with NSAI recommendation; the submitter agreed with the abemaciclib in combination with fulvestrant recommendation and requested that it be maintained in pERC's Final Recommendation. The registered clinicians agreed in part and supported early conversion. CBCN agreed in part and supported early conversion; CBCN agreed with the recommendations except for the requirement that endocrine naive/sensitive patients receiving abemaciclib in combination with a nonsteroidal aromatase inhibitor must be unable to tolerate or have a contraindication to available CDK4/6 inhibitors in order to access abemaciclib. Rethink Breast Cancer agreed in part and did not support early conversion; Rethink Breast Cancer requested clarification on the eligible endocrine naive population. As a result, pERC deliberated on the feedback upon reconsideration for abemaciclib in combination with a non-steroidal aromatase inhibitor (NSAI) (i.e., anastrozole or letrozole) for the treatment of HR+, HER2- advanced or metastatic breast cancer in patients as initial endocrine-based therapy and abemaciclib in combination with fulvestrant in patients with disease progression following endocrine therapy.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the efficacy and safety of abemaciclib for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2—) advanced or metastatic breast cancer:

- In combination with an aromatase inhibitor in postmenopausal women as initial endocrine-based therapy. (first-line systemic therapy/endocrine sensitive).
- In combination with fulvestrant in women with disease progression following endocrine therapy. Premenopausal or perimenopausal women must also be treated with a gonadotropin-releasing hormone agonist (endocrine-resistant).

The pCODR review also provided contextual information on supplemental issues most relevant to the pCODR review and to the PAG:

- Summary and critical appraisal of the manufacturer-submitted NMA of interventions for locoregionally recurrent or metastatic breast cancer patients comparable to the MONARCH 3 trial patient population (first-line systemic therapy/endocrine sensitive).
- Summary and critical appraisal of the manufacturer-submitted NMA of interventions for advanced or metastatic breast cancer patients comparable to the MONARCH 2 trial patient population (endocrine-resistant).

First-Line Systemic Therapy/Endocrine Sensitive

Included: MONARCH 3 (First-Line Systemic Therapy/Endocrine Sensitive)

The pCODR systematic review included MONARCH 3: a phase III, multi-centre, randomized, double-blind, placebo-controlled study of abemaciclib plus NSAI or placebo plus NSAI in postmenopausal women with HR+, HER2− advanced or metastatic breast cancer who had not received any previous systemic therapy in the advanced/metastatic setting. Eligible patients were randomized to receive abemaciclib plus NSAI (anastrozole or letrozole per physician's choice) or placebo plus NSAI.

A total of 493 patients were included in the MONARCH 3 trial, with 328 patients in the abemaciclib plus NSAI arm and 165 patients in the placebo plus NSAI arm.

The primary efficacy end point was investigator-assessed PFS; according to Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1). Key secondary end points included objective response rate (ORR), duration of response, OS, and clinical benefit rate (CBR).

Patient populations: Female patients with HR+, HER2— advanced or metastatic breast cancer

Key eligibility criteria included:

- ≥ 18 years of age
- female, postmenopausal age ≥ 60 or; age ≤ 60 and amenorrhea for ≥12 months with FSH + estradiol in postmenopausal range; or prior bilateral oophorectomy
- HR+, HER2— advanced or metastatic breast cancer
- ECOG PS ≤ 1
- measurable disease (by RECIST v1.1) or non-measurable bone-only disease
- locoregionally recurrent or metastatic disease not amenable to curative surgery or radiation therapy.

Patients were excluded if:

- they received prior (neo)adjuvant endocrine therapy (e.g., anti-estrogens or aromatase inhibitors) with a disease-free interval ≤12 months from completion of treatment.

Key efficacy results: Immature OS, clinically meaningful and statistically significant PFS

The key efficacy outcomes deliberated on by pERC included PFS and OS.

PFS: As of the January 31, 2017 data cut-off date, after a median follow-up duration of 17.8 months, a total of 108 patients (32.9%) in the abemaciclib plus NSAI arm and 86 patients (52.1%) in the placebo plus NSAI arm had a PFS event. The median PFS was not reached in the abemaciclib plus NSAI arm and was 14.7 months with placebo plus NSAI (HR = 0.54; 95% CI, 0.41 to 0.72; *P* = 0.000021). The results of the blinded central analysis were consistent with those of the primary analysis (HR = 0.51; 95% CI, 0.36 to 0.72; *P* = 0.000102). The PFS benefit was maintained across pre-defined patient subgroups.

At the November 7, 2017 data cut-off, after a median follow-up duration of 26.73 months, 246 investigator-assessed PFS events had occurred (138 [42.1%] events in the abemaciclib plus NSAI arm and 108 [65.5%] events in the placebo plus NSAI arm). The median PFS was 28.18 months in the abemaciclib plus NSAI arm compared with 14.76 months in the placebo+ NSAI arm (HR = 0.540; 95% CI 0.418, 0.698); *P* = 0.000002). In the subgroup analysis, PFS benefit was maintained across the pre-defined patient subgroups.

OS: At the January 31, 2017 data cut-off date, OS results were immature, with a total of 49 deaths (32 deaths [9.8%] in the abemaciclib plus NSAI arm and 17 deaths [10.3%] in the placebo plus NSAI arm). The median OS was not reached in either of the arms. The final OS analysis is planned to be performed after the occurrence of 315 death events.

Patient-reported outcomes: Clinically meaningful and statistically significant difference in diarrhea

No peer-reviewed publications reporting on the QoL data from the MONARCH 3 trial were identified in this pCODR review. The following data have been extracted from a conference abstract and the related poster presentation that was provided by the submitter:

A clinically meaningful (≥ 10 points) and statistically significant worsening in diarrhea was reported in the abemaciclib plus NSAI arm. There was a statistically significant and clinically meaningful worsening in EORTC QlQ-C30 diarrhea symptom score in abemaciclib-treated patients (mean change = 18.68; 95% CI, 15.13 to 22.22; *P* < 0.001). Changes from baseline in the following symptom scores were statistically different (but not clinically meaningful) between the two study arms, all favouring the placebo arm: nausea and vomiting (mean change = 2.77; 95% CI, 0.58 to 4.97; *P* = 0.013), appetite loss (mean change = 4.03; 95% CI, 0.31 to 7.74; *P* = 0.034), and fatigue (mean change = 4.96; 95% CI, 1.58 to 8.35; *P* = 0.004). In addition, a statistically significant worsening was observed with abemaciclib in Global Health status, role functioning, social functioning, body image, and the composite score for the systemic therapy symptoms.

Limitations: Immature OS data, direct comparison to NSAI alone, limitations to indirect comparison

- Mature OS data were not available at the time of interim analysis. Longer-term follow-up is needed to determine the effect of adding abemaciclib to an NSAI on OS.
- The results of the subgroup analysis in MONARCH 3 trial should be interpreted with attention to the fact that the study was not powered to detect differences in the specific subgroups. Therefore, the subgroup analyses of the primary outcome are considered descriptive.
- A relative high number of patients (> 80%) had one or more major protocol deviations. This proportion was higher in the abemaciclib plus NSAI arm (84.1%) than the placebo plus NSAI arm (77.6%). However, the deviations were generally well balanced between the two study groups and seem to be less likely to impact the study end points.
- pERC was not confident in the results of the NMA due to the following limitations: heterogeneity of study patient populations, immature OS data, and exclusion of QoL and safety outcomes related to diarrhea.

Safety: Considerable, but manageable toxicity

As of the January 31, 2017 data cut-off date, after a median follow-up of 17.8 months, 98.8% of patients in the abemaciclib plus NSAI arm and 94.4% of those in the placebo plus NSAI arm had at least one reported treatment-emergent AE. In the abemaciclib plus NSAI arm, the most common AEs (any grade reported by
≥ 30% of the patients) included diarrhea, neutropenia, fatigue, nausea, anemia, abdominal pain, and vomiting. Grade 3 and 4 treatment-emergent AEs were reported in 61.8% of abemaciclib-treated patients and 26.1% of placebo-treated patients. Serious AEs were reported in 31.2% of patients in the abemaciclib plus NSAI arm and 16.8% of those in the placebo plus NSAI arm. The withdrawal rate due to AEs in the abemaciclib plus NSAI arm (16.5%) was higher than that in the placebo plus NSAI arm (3.1%). Death due to an AE was reported for eight patients (2.4%) receiving abemaciclib plus NSAI and one patient (0.4%) receiving placebo plus NSAI.

At the time of the 90-day safety update (August 11, 2017), a total of 16 deaths were reported: 13 deaths with abemaciclib plus NSAI and three with placebo plus NSAI. The updated results showed no new safety signals.

As of November 7, 2017, a total of 323 patients (98.8%) in the abemaciclib plus NSAI arm and 152 patients (94.4%) in the placebo plus NSAI arm were reported with at least one AE. Diarrhea was the most common AE in the abemaciclib-treated patients (82.3% versus 32.3% in the placebo arm). Neutropenia occurred in 43.7% of abemaciclib-treated patients compared with 1.9% in the placebo arm. Dose reductions due to AEs occurred for 46.5% of patients receiving abemaciclib plus NSAI and 6.2% of those receiving placebo plus NSAI. Overall, 25.1% of patients in the abemaciclib plus NSAI arm and 4.3% of those in the placebo plus NSAI arm discontinued any study drug due to an AE. A total of 18 deaths were reported: 15 deaths with abemaciclib plus NSAI (11 due to AEs) and three (1.9%) with placebo plus NSAI (two were due to AEs).

Need and burden of illness: Need for patients intolerant to therapy

Breast cancer is the most common diagnosed malignancy in Canadian women, with an estimated 26,300 new cases and 5,000 deaths in 2017. While many women diagnosed with early stage breast cancer will be cured with treatment, some women will experience a relapse of their breast cancer (metastatic spread to other organs), with an additional 5% to 10% of women who will present with de novo metastatic breast cancer. Advanced or metastatic breast cancer remains incurable and is treated systematically with

palliative intent. In the setting of metastatic disease, median life expectancy is approximately two to three years. pERC acknowledged that treatment options are available in the first-line setting, and more specifically pERC noted an available, funded CDK 4/6 inhibitor (palbociclib plus letrozole). pERC recognized that intolerance (i.e., unmanageable toxicity) to CDK 4/6 inhibitors may occur; and therefore, pERC agreed that there is a need for abemaciclib plus NSAI in patients who are intolerant to other available CDK 4/6 inhibitors.

Registered clinician input: another funded option

While current treatment for postmenopausal patients diagnosed with hormone receptor positive (HR+) and HER2-negative metastatic breast cancer includes palbociclib plus letrozole, it was noted that abemaciclib plus letrozole or anastrozole would serve as another funded option particularly in the setting of intolerance to first-line palbociclib.

Endocrine Resistant

Included: MONARCH 2 (Endocrine Resistant)

The pCODR systematic review included the MONARCH 2 trial: a phase III, multi-centre, randomized, double-blind, placebo-controlled study of fulvestrant with or without abemaciclib in women with HR+, HER2− advanced or metastatic breast cancer whose disease had progressed on previous endocrine therapy in the metastatic setting. Eligible patients were randomized in a 2:1 ratio to receive abemaciclib plus fulvestrant or placebo plus fulvestrant (28-day cycles). All premenopausal or perimenopausal women were also treated with a gonadotropin-releasing hormone agonist.

A total of 669 patients with endocrine-resistant disease were enrolled in the trial.

The primary efficacy end point was investigator-assessed PFS (according to RECIST version 1.1). Key secondary end points included ORR, duration of response, OS, and CBR.

Patient population: Female patients with HR+, HER2− advanced or metastatic breast cancer

Key eligibility criteria included:

- ≥ 18 years of age
- female, any menopausal status
- HR+, HER2- advanced or metastatic breast cancer
- ECOG PS ≤ 1
- measurable disease (by RECIST v1.1) or non-measurable bone-only disease
- progressed while receiving prior endocrine therapy for advanced breast cancer.

Key efficacy results: Immature OS, clinically meaningful and statistically significant PFS

The key efficacy outcome deliberated on by pERC included PFS and OS.

PFS: At the February 14, 2017data cut-off date, after a median follow-up duration of 19.5 months, a total of 222 patients (49.8%) in the abemaciclib plus fulvestrant arm and 157 patients (70.4%) in the placebo plus fulvestrant arm had a PFS event. The median PFS was 16.4 months with abemaciclib plus fulvestrant and 9.3 months with placebo plus fulvestrant (hazard ratio = 0.55; 95% confidence interval [CI], 0.45 to 0.68; $P < 0.001$). The results of the blinded central analysis were consistent with those of the primary analysis (HR = 0.460; 95% CI, 0.363 to 0.584; $P < 0.001$). The PFS benefit was maintained across the pre-defined patient subgroups.

OS: At the February 14, 2017 data cut-off date, OS results were immature, with a total of 133 deaths (85 deaths [19.1%] in the abemaciclib plus fulvestrant arm and 48 deaths [21.5%] in the placebo plus fulvestrant arm). The median OS was not reached in either of the arms. The final OS analysis is planned to be performed after the occurrence of 441 death events.

Patient-reported outcomes: Clinically meaningful and statistically significant difference in diarrhea

No peer-reviewed publications reporting on the quality of life data from the MONARCH 2 trial were identified in this pCODR review. The following data have been extracted from a conference abstract and its related poster presentation that was provided by the submitter:

Treatment with abemaciclib plus fulvestrant delayed the median time to worsening of pain by approximately five months (16.8 months in the abemaciclib arm versus 11.9 months in the placebo arm). However, this difference was not statistically significant (HR = 0.900; 95% CI, 0.707 to 1.145; $P = 0.40$). When compared with placebo plus fulvestrant, abemaciclib plus fulvestrant resulted in a statistically

significant worsening in the following symptoms from baseline: nausea and vomiting (mean change = 3.42; 95% CI, 1.68 to 5.15; *P* < 0.001), appetite loss (mean change = 5.31; 95% CI, 2.49 to 8.13; *P* < 0.001), and diarrhea (mean change = 24.64; 95% CI, 21.58 to 27.71; *P* < 0.001). There was also a clinically meaningful (≥ 10 points) difference between the two groups in terms of change from the baseline in diarrhea score, favouring placebo.

Limitations: Immature OS data, direct comparison to fulvestrant alone, limitations to indirect comparison

The key limitations of the MONARCH 2 trial included:

- The absence of mature OS data at the time of interim analysis.
- After protocol amendment b (March 30, 2015), MONARCH 2 excluded all endocrine therapy naive patients (i.e., first-line systemic therapy patients) from the intention-to-treat(ITT) analysis and focused the study objectives on evaluating treatment effects in endocrine-resistant patients. Therefore, the effects of abemaciclib plus fulvestrant in the endocrine therapy naive patients (i.e., first-line systemic therapy patient) cannot be evaluated in this trial.
- Duration of therapy was longer in the experimental as compared with the control arm (13 months and nine months respectively) with a median number of cycles of abemaciclib received per patient of 15 as compared with nine cycles in the control arm. Dose intensity was lower in the abemaciclib plus fulvestrant arm (median 273 mg/day and mean 261 mg/day in the experimental arm versus median 298 mg/day and mean 309 mg/day in the placebo plus fulvestrant arm).
- A relative high number of patients (> 80%) had one or more major protocol deviations, with the "*key measurements not collected properly*" and "*incorrect stratification factors for IWRS*" being the most frequent types of protocol deviation. However, the deviations are well balanced and seem to be less likely to impact the study end points.
- pERC was not confident in the results of the NMA due to the following limitations: heterogeneity of study patient populations, immature OS data, and exclusion of QoL and safety outcomes related to diarrhea.

Safety: Considerable, but manageable toxicity

As of the February 14,2017 data cut-off date, after a median follow-up of 19.5 months, 98.6% of patients in the abemaciclib plus fulvestrant arm and 89.2% of those in the placebo plus fulvestrant arm had at least one reported treatment-emergent AE. The most common AEs (any grade reported by ≥ 10% of the patients) in the abemaciclib plus fulvestrant arm included: diarrhea, neutropenia, nausea, fatigue, abdominal pain, anemia, leukopenia, vomiting, headache, dysgeusia, and alopecia. Grade 3 and 4 treatment-emergent AEs were reported for 62.6% of patients receiving abemaciclib plus fulvestrant and 23.8% of those who received placebo plus fulvestrant. In the MONARCH 2 trial, 22.4% of patients in the abemaciclib plus fulvestrant arm and 10.8% of those in the placebo plus fulvestrant arm experienced at least one serious AE. The frequency of the withdrawal rate due to AEs was 8.6% in the abemaciclib plus fulvestrant arm and 3.1% in the placebo+ fulvestrant arm. Deaths due to AEs were reported in six patients (1.4%), patients receiving abemaciclib plus fulvestrant, and one patient (0.4%) receiving placebo plus fulvestrant.

Need and Burden of Illness: Need for patients intolerant to therapy

Breast cancer is the most common diagnosed malignancy in Canadian women, with an estimated 26,300 new cases and 5,000 deaths in 2017. While many women diagnosed with early stage breast cancer will be cured with treatment, some women will experience a relapse of their breast cancer (metastatic spread to other organs), with an additional 5% to 10% of women who will present with de novo metastatic breast cancer. Advanced or metastatic breast cancer (MBC) remains incurable and is treated systematically with palliative intent. In the setting of metastatic disease, median life expectancy is approximately two to three years. pERC acknowledged that treatment options for patients with disease progression following endocrine therapy are available; pERC also noted that it recently made a recommendation for a CDK 4/6 inhibitor (palbociclib plus fulvestrant) for patients whose disease progressed after prior endocrine therapy. pERC recognized that intolerance (i.e., unmanageable toxicity) to CDK 4/6 inhibitors may occur; and therefore, pERC agreed that there is a need for abemaciclib plus fulvestrant for patients who are intolerant to other available CDK 4/6 inhibitors.

Registered clinician input: Another funded option

Clinicians suggested that the combination of abemaciclib and fulvestrant is an option for patients with metastatic HR+, HER2–MBC who have progressed on previous endocrine therapy, which is considered (by the registered clinicians) as more effective than switching to another form of endocrine monotherapy.

PATIENT-BASED VALUES

Values of Patients with Advanced or MBC: Extended OS and PFS, QoL, and Choice
Patient input was received from Rethink Breast Cancer and the CBCN. Patients who completed Rethink Breast Cancer's survey considered controlling disease and extending life expectancy to be the most important results to obtain, thus placing emphasis on prioritizing health outcomes over immediate concerns like reducing disease symptoms or managing side effects. Similarly, patients who completed the survey by CBCN expressed the willingness to try new treatments even if benefits were as little as a six-month extension of PFS. Furthermore, the CBCN stated that patients want treatments that provide them with a good quality of life and concluded that based on results from the clinical trials, patients treated with abemaciclib tolerated the treatment well. Overall, patients with MBC value a delay in disease progression, increased life expectancy, manageable side effects, additional treatment choice, lack of detriment in quality of life, and lower out of pocket expenses.

Patient experiences and values on abemaciclib combination: Patients Experienced Diarrhea, Patients Recommend Abemaciclib

Two postmenopausal women indicated they were treated with abemaciclib in combination with fulvestrant following disease progression. One postmenopausal patient was treated with abemaciclib in combination with an aromatase inhibitor as initial endocrine-based therapy. The most commonly reported side effect associated with abemaciclib therapy was diarrhea, by all three respondents. Other reported side effects included: loss of appetite, abdominal pain, nausea and gas. There was consensus among the three patients to recommend abemaciclib to other patients with advanced or MBC.

While CBCN was unable to connect with Canadian patients who had experience with abemaciclib, previous surveys and submissions revealed that patients with this stage of disease should have access to many treatment options as it is a heterogeneous disease. Treatments that provide a good quality of life are also important and data from clinical trials showed that abemaciclib seemed to be well tolerated by patients.

ECONOMIC EVALUATION

First-Line Systemic Therapy/Endocrine Sensitive

Economic model submitted: Cost-utility analysis and cost-effectiveness analysis
The manufacturer-submitted cost-utility analysis and cost-effectiveness analysis compared the combination of abemaciclib plus NSAI (including anastrozole or letrozole), ribociclib plus NSAI, palbociclib plus NSAI with NSAI alone for the treatment of advanced breast cancer in patients with no prior therapy over a time horizon of 15 years.

Basis of the economic model: Markov model
The submitted model was a Markov model with three health states including PFS for the first-line, post-progression survival, and death. Costs and outcomes following progression were attributed at the point of relapse based on the calculation of "a fixed pay-off." Key data sources included the MONARCH 3 trial and an NMA report from the submitter.

Drug Costs: Cost of Abemaciclib Plus NSAI During a 28-Day Course of Treatment — $5,000

Cost of abemaciclib	• $0.63 per mg (150 mg per tablet) • $190.40 per day • $5,331.20 per 28-day course
Cost of ribociclib	• $0.50 per mg (200 mg per tablet) • $223.20 per day • $6,249.60 per 28-day course
Cost of palbociclib	• $2.03 per mg (125 mg per tablet) • $190.43 per day • $5,332.11 per 28-day course

Cost of NSAI: letrozole Cost of NSAI: anastrozole ** Price Source: Quintiles IMS Delta PA accessed March 2018*	• $0.55 per mg (2.5 mg per tablet) • $1.33 per day • $38.58 per 28-day course • $1.27 per mg (1 mg per tablet) • $1.27 per day • $35.64 per 28-day course
Cost of abemaciclib plus NSAI (letrozole) Cost of abemaciclib plus NSAI (anastrozole)	• $1.19 per mg • $96.58 per day • $5,408.37 per 28-day course • $1.91 per mg • $96.47 per day • $5,402.48 per 28-day course

Cost-effectiveness estimates: Focus on abemaciclib plus NSAI compared with NSAI alone
The EGP's main reanalysis focused on abemaciclib plus NSAI compared with NSAI alone given the limitations of the NMA. pERC agreed with this approach and concluded that the results of the cost-effectiveness of abemaciclib plus NSAI compared with palbociclib plus NSAI, and ribociclib plus NSAI need to be interpreted with caution.

Endocrine Resistant

Economic model submitted: Cost-utility analysis and cost-effectiveness analysis
The cost-utility analysis and cost-effectiveness analysis submitted to pCODR by the manufacturer that compared the combination of abemaciclib plus fulvestrant, exemestane plus everolimus, palbociclib plus fulvestrant with fulvestrant for the treatment of breast cancer in patients with disease progression or after prior endocrine therapy over a time horizon of five years.

Basis of the economic model: partition-survival model
The submitted model was a partition-survival model with three health states including PFS, post-progression survival and death. Key data sources included the MONARCH 2 trial and the NMA report from the submitter.

Drug costs: Cost of abemaciclib plus fulvestrant during a 28-day course of treatment — ~$6,500 (cycle two onward)

Cost of abemeciclib	• $0.63 per mg (150 mg per tablet) • $190.40 per day • $5,331.20 per 28-day course
Cost of exemestane Cost of everolimus Cost of palbociclib Cost of fulvestrant ** Price Source: Quintiles IMS Delta PA accessed March 2018*	• $0.05 per mg (25 mg per tablet) • $1.33 per day • $37.24 per 28-day course • $20.13 per mg (10 mg per tablet) • $201.25 per day • $5,635 per 28-day course • $2.03 per mg (125 mg per tablet) • $190.43 per day • $5,332.11 per 28-day course • $2.33 per mg (250 mg per mL) • $41.64 per day • $1,165.80 per 28-day course for cycle 2 onwards

	• Cost for cycle 1 (including loading dose) = $2,331.60
Cost of abemaciclib plus fulvestrant	• $2.97 per mg • $232.04 per day • $6,497.00 per 28-day course for cycle 2 onwards • Cost for cycle 1 (including fulvestrant loading dose) = $7,662.80

Cost-effectiveness estimates: Focus on abemaciclib plus fulvestrant compared with fulvestrant alone

The EGP's main reanalysis focused on abemaciclib plus fulvestrant compared with fulvestrant alone given the limitations of the NMA. pERC agreed with this approach and concluded that the results of the cost-effectiveness of abemaciclib plus fulvestrant compared with palbociclib plus fulvestrant and exemestane plus everolimus need to be interpreted with caution.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact influenced by uptake rate of abemaciclib among other factors

First-Line Systemic Therapy/Endocrine-Sensitive

The factors that most influence the BIA include the number of treatment cycles, the ratio of used and planned dose intensity, and the variation in the uptake rate of abemaciclib plus NSAI. Replacing the number of treatment cycles by the mean progression –free survival decreased the budget impact. Assuming 100% of the ratio of used and planned dose intensity for all drugs increased budget impact due to increased drug spending in all treatments. Varying the uptake rates of abemaciclib plus NSAI had minimal changes in the base-case results. However, changes in the market shares of palbociclib plus NSAI and ribociclib plus NSAI had a substantial impact on the three-year budget due to their large acquisition costs. The larger the market share of palbociclib plus NSAI and ribociclib plus NSAI that abemaciclib plus NSAI can replace, the smaller the budgetary impact of abemaciclib plus NSAI to the health care system.

Endocrine Resistant

The factors that most influence the BIA include the number of treatment cycles, the ratio of used and planned dose intensity, and the variation in the uptake rate of abemaciclib plus fulvestrant. Replacing the number of treatment cycles by the mean PFS decreased the budgetary impact. Applying the ratio of used and planned dose intensity observed in each primary RCT to the model decreased budget impact substantially. Varying the uptake rate of abemaciclib plus fulvestrant had minimal impact on the base-case results. However, changes in the market shares of palbociclib plus fulvestrant, because of an increased uptake of abemaciclib plus fulvestrant, had a substantial impact on the three-year budgetary impact. The larger the market share of palbociclib plus fulvestrant that abemaciclib plus fulvestrant can replace, the smaller the budgetary impact of abemaciclib plus fulvestrant to the health care system.

Refer to the summary table in Appendix 1 for more details regarding the consideration for implementation.

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. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation for abemaciclib plus NSAI, except:

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

All members participated in deliberations and voting on the Initial Recommendation for abemaciclib plus fulvestrant, except:

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

All members participated in deliberations and voting on the Final Recommendation for abemaciclib plus NSAI, except:

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

All members participated in deliberations and voting on the Final Recommendation for abemaciclib plus fulvestrant, except:

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

Avoidance of conflicts of interest

All members of the pERC 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 abemaciclib plus NSAI and abemaciclib plus fulvestrant, through their declarations, five members had a real, potential, or perceived conflict and based on 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 PAG 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 the pCODR Expert Review Committee 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.

Disclaimer

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

PAG implementation Questions/Notes	pERC
Currently Funded Treatments *First-line systemic therapy/endocrine sensitive advanced breast cancer* • PAG is seeking information comparing abemaciclib with ribociclib and palbociclib — is one better than the others and under what circumstances would abemaciclib be preferred to ribociclib or palbociclib or vice-versa? • PAG is seeking information on the use of abemaciclib with aromatase inhibitors other than letrozole or anastrozole. *Endocrine-resistant advanced breast cancer* • Fulvestrant is not publicly funded in any provinces for MBC. PAG is seeking information on data comparing abemaciclib plus fulvestrant with currently available treatments. • PAG also noted that palbociclib-fulvestrant is currently undergoing pCODR review. PAG would like guidance on how abemaciclib-fulvestrant compares with palbociclib-fulvestrant — is one better than the others and under what circumstances would abemaciclib be preferred to palbociclib or vice-versa?	**Currently Funded Treatments** *First-line systemic therapy/endocrine sensitive advanced breast cancer* • pERC recommends abemaciclib plus NSAI for patients intolerant to other available CDK 4/6 inhibitors (e.g., ribociclib and palbociclib). • pERC agreed with CGP in that the combination of abemaciclib with an NSAI should be limited to either anastrozole or letrozole based on the current evidence. Upon reconsideration, pERC discussed the feedback from registered clinicians, and in acknowledging consistency with the funded CDK 4/6 inhibitor, pERC noted that it would be acceptable to extend funding to the use of abemaciclib with any AI, instead of limiting to letrozole and anastrozole. *Endocrine-resistant advanced breast cancer* • pERC acknowledged that fulvestrant is not publicly funded in any provinces for MBC. pERC also noted that pERC recently made a recommendation for palbociclib plus fulvestrant in a similar population; however, this drug is not currently publicly funded in any Canadian jurisdiction. • Through the NMA, the PFS of palbociclib plus fulvestrant and abemaciclib plus fulvestrant is likely similar. There is insufficient evidence to comment on the OS between these agents.
Eligible Patient Population *First-line systemic therapy/endocrine sensitive advanced breast cancer* • PAG is seeking information on whether results with abemaciclib would be generalizable to premenopausal or perimenopausal women who would be treated with an LHRH agonist to induce postmenopausal status. • The MONARCH 3 trial excluded patients currently receiving or who have previously received chemotherapy for locoregionally recurrent or MBC; PAG is seeking confirmation that these subgroups of patients would not be eligible for treatment with abemaciclib. *Endocrine-resistant advanced breast cancer* • PAG commented that there may be pressure from oncologists/patients to use	**Eligible Patient Population** *First-line systemic therapy/endocrine sensitive advanced breast cancer* • pERC agreed with the CGP that women rendered postmenopausal (either chemically or surgically) would be eligible. Upon reconsideration, pERC acknowledged PAG's request to reiterate woman who were rendered postmenopausal (either chemically or surgically) would be eligible in the pERC Recommendation of this document. • pERC agreed with the CGP that for patients who have progressed on prior endocrine or systemic therapy, they would not be eligible. Additionally, patients had to have at least 12 months disease-free interval after the completion of adjuvant hormone therapy.

abemaciclib plus an aromatase inhibitor (letrozole/anastrozole) as subsequent line even though there may not be data in the previously treated advanced breast cancer setting.
 	
Overall (First-line systemic therapy/endocrine resistant)
• The MONARCH 2 and 3 trials excluded inflammatory breast cancer patients. PAG is also seeking information on whether abemaciclib results would be generalizable to men.
• If recommended for funding, PAG is seeking guidance on the appropriateness of:
  ○ adding abemaciclib for patients who are already on an endocrine therapy (e.g., anastrozole or letrozole if endocrine naive or fulvestrant if endocrine resistant) but not yet progressed
  ○ switching patients who are already on other endocrine therapy but not yet progressed to abemaciclib
  ○ switching abemaciclib with ribociclib or palbociclib for the respective indications, if the patient is intolerant to one
  ○ continuing treatment if there is oligoprogression.
• In addition, PAG is seeking information on post-progression therapies and the impact of those therapies on cost-effectiveness, particularly on the use of everolimus and exemestane after abemaciclib compared with use of chemotherapy after abemaciclib.
	• Upon reconsideration, pERC discussed PAG's request regarding the eligibility of patients. pERC noted that patients who had previously been treated with chemotherapy (but were endocrine naive/sensitive) would not be eligible for abemaciclib since the MONARCH 3 study excluded any patients who previously had chemotherapy for advanced breast cancer.
	
	Endocrine-resistant advanced breast cancer
	• There is no evidence to inform a recommendation for abemaciclib plus NSAI in subsequent lines of therapy.
	
	Overall (First-line systemic therapy/endocrine resistant)
	• pERC agreed with CGP that the MONARCH 3 trial is not generalizable to patients with inflammatory breast cancer or uncontrolled central nervous system metastases. However in some instances of metastatic disease, it may make sense to use abemaciclib plus fulvestrant in later lines.
	• pERC agrees with the CGP that these trial results would be generalizable to men with HR+, HER2- advanced breast cancer.
	
	• If recommended for funding:
	  ○ Adding abemaciclib for patients who are already on an endocrine therapy (e.g., anastrozole or letrozole if endocrine naive [i.e., First-line systemic therapy/endocrine-sensitive] or fulvestrant if endocrine resistant) but have not yet progressed — pERC's recommendation is limited to patients intolerant to available CDK-4/6 inhibitors (in the first-line setting), since fulvestrant is not a funded treatment option.
	  ○ Upon reconsideration, pERC addressed PAG's question about a time-limited recommendation for patients already on fulvestrant, given that patients have been able to receive compassionate supply fulvestrant; pERC noted that this approach would be appropriate, given that patients have been able to receive compassionate supply fulvestrant.
	  ○ Switching patients who are already on other endocrine therapy but have not yet progressed to abemaciclib - appropriate for patients intolerant to available CDK-4/6 inhibitors.
	  ○ Switching abemaciclib with ribociclib or palbociclib for the respective

	indications, if patient is intolerant to one. ○ Continuing treatment if there is oligoprogression — pERC agreed with CGP in that there is no clear guidance from the literature on the continued use of abemaciclib at the time of oligoprogression. • Given the limitations of the NMA and economic model, pERC was unable to comment on the impact of post-progression therapies on cost-effectiveness.
Implementation Factors • PAG noted that patients on aromatase inhibitors may not be seen by oncologists on a monthly basis. However, monthly monitoring may be needed due to the high incidence of neutropenia and gastrointestinal-related toxicity and due to drug interactions. • The increased dosing of abemaciclib (twice daily) may be less convenient than once daily palbociclib or ribociclib. However, the abemaciclib's daily schedule without days off treatment may be easier for patients. • At the time of this PAG input, fulvestrant is not funded in any provinces, which is a barrier to implementation. Fulvestrant is available as 250 mg pre-filled syringes, which is an enabler as pharmacy preparation is not required and there is no wastage concern. PAG noted that fulvestrant must be refrigerated and since fulvestrant comes in a large box, fridge space can become a concern. Fulvestrant requires nursing resources to administer the intramuscular injection (2 x 250 mg injections). The volume and viscosity of fulvestrant can be a challenge for health care professionals. Patients would need monthly treatment visits, which require incremental resources over patients who receive oral endocrine therapy. • As abemaciclib may be added on to existing therapy, there may be a large budget impact given the large number of patients, the high cost of the combination compared with aromatase inhibitors alone, and the additional pharmacy resources required.	**Implementation Factors** • Given the risks of toxicity with abemaciclib plus NSAI, pERC noted that jurisdictions should consider developing guidelines or processes to monitor and manage toxicity in patients who receive abemaciclib. • pERC acknowledged the different administration schedule compared with other available therapy (twice daily versus once daily). • pERC acknowledged the impact of abemaciclib on resources and BIA and this is described in the Summary of Deliberations.
Sequencing and Priority of Treatments • PAG is seeking guidance on the appropriate sequencing of all available treatments for HR+, HER2- advanced breast cancer. ○ What treatments can patients receive following abemaciclib plus an aromatase inhibitor? Or following abemaciclib plus fulvestrant? ○ How should everolimus plus	pERC noted that there is no clinical trial evidence to inform the optimal sequencing of treatments after abemaciclib plus a NSAI or abemaciclib plus fulvestrant.

exemestane be sequenced?	

AI = aromatase inhibitor; BIA = budget impact analysis; CDK = cyclin-dependent kinase; CGP = Clinical Guidance Panel; HR+ = hormone receptor -positive; HER2- = human epidermal growth factor receptor 2 -negative; LHRH = luteinizing hormone-releasing hormone; MBC = metastatic breast cancer; NMA = network meta-analysis; NSAI = non-steroidal aromatase inhibitor; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.