pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL 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.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug: Ribociclib (Kisqali)

Submitted Funding Request:
In combination with letrozole for the treatment of post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as an initial endocrine-based therapy

Submitted by:
Novartis Pharmaceuticals Canada Inc.

Manufactured by:
Novartis Pharmaceuticals Canada Inc.

NOC Date:
March 2, 2018

Submission Date:
October 17, 2017

Initial Recommendation Issued:
March 29, 2018

Approximate per Patient Drug Costs, per Month (28 Days)	**Ribociclib costs:**
Submitted list price Ribociclib: $99.20 per 200 mg tablet	• $6,249.99 per 28-day course

pERC RECOMMENDATION

pERC conditionally recommends reimbursement of ribociclib (Kisqali) in combination with letrozole for the treatment of post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as an initial endocrine-based therapy, only if the following conditions are met:

- cost-effectiveness being improved to an acceptable level
- feasibility of adoption (budget impact) being addressed.

If the aforementioned conditions cannot be met, pERC does not recommend reimbursement of ribociclib plus letrozole. Treatment should continue until unacceptable toxicity or disease progression. Patients should have good performance status and not be resistant to prior (neo)adjuvant nonsteroidal aromatase inhibitor (NSAI) therapy (i.e., disease-free for at least a year from the completion of prior adjuvant NSAI therapy), nor have active or uncontrolled metastases to the central nervous system.

pERC made this recommendation because it was satisfied that, compared with letrozole monotherapy, there is a moderate net clinical

	benefit of ribociclib plus letrozole, based on statistically significant and clinically meaningful improvements in progression-free survival (PFS), a manageable but not insignificant toxicity profile, and no significant detriment in quality of life (QoL). However, the Committee's assessment of net clinical benefit was tempered by the lack of evidence, at this time, demonstrating a statistically significant improvement in overall survival (OS). pERC agreed that ribociclib plus letrozole aligns with patient values because of the delay in disease progression, oral route of administration, manageable side effects, additional treatment choice, and lack of detriment in QoL. pERC concluded that, at the submitted price, ribociclib plus letrozole is not cost-effective compared with letrozole monotherapy. pERC highlighted that the potential budget impact of ribociclib plus letrozole was underestimated and would be substantial. pERC had significant concerns about the capacity of jurisdictions to implement ribociclib in combination with letrozole due to the potentially large number of patients eligible for this treatment and the additional health care resources required to monitor and manage toxicities (e.g., frequent clinic visits, blood work, electrocardiograms (ECGs), and nursing and pharmacy time) compared to treatment with letrozole alone.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness and Decrease Budget Impact** Given that pERC was satisfied that there is a moderate net clinical benefit of ribociclib plus letrozole, jurisdictions may want to consider pricing arrangements that would improve the cost-effectiveness and budget impact of ribociclib plus letrozole to an acceptable level. pERC noted that a substantial reduction in the price of ribociclib would be required in order to improve the cost-effectiveness to an acceptable level and to decrease the predicted substantial budget impact. **Time-Limited Need for Ribociclib Plus Letrozole in Patients Currently Receiving First-Line Letrozole Monotherapy** At the time of implementing a funding recommendation for ribociclib plus letrozole, jurisdictions may want to consider addressing the short-term, time-limited need to offer ribociclib plus letrozole to patients who are not resistant to (neo)adjuvant nonsteroidal aromatase inhibitor (NSAI) therapy (i.e., disease-free for at least a year from the completion of prior NSAI therapy), and who recently started letrozole monotherapy for the treatment of post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as an initial endocrine-based therapy. **Generalizability of Results to Male patients With HR-Positive, HER2-Negative Advanced or Metastatic Breast Cancer** pERC noted that generalizing the MONALEESA-2 trial results to male patients might be reasonable but as males were not included in the trial, direct evidence is lacking at this time. It is unlikely that there will be trials specifically designed for this small group of patients and there is no biological rationale to assume that outcomes of ribociclib plus letrozole therapy would be different between male and female patients with HR-positive, HER2-negative advanced or metastatic breast cancer.

Choice of Aromatase Inhibitor in Combination With Ribociclib
pERC agreed that ribociclib should be used in combination with letrozole based on the available randomized controlled trial (RCT) evidence. However, the Committee felt that, in patients with intolerance to letrozole, it would be reasonable to use another aromatase inhibitor in combination with ribociclib if no disease progression had occurred during letrozole plus ribociclib.

Sequencing of Treatments in HR-Positive, HER2-Negative Advanced or Metastatic Breast Cancer
pERC was unable to make an informed recommendation on the optimal sequencing of ribociclib plus letrozole and everolimus plus exemestane, as the Committee noted that, as yet, there is no evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of ribociclib plus letrozole and noted that a national approach to developing evidence-based clinical practice guidelines would be of value.

Oral Administration of Ribociclib
pERC noted that, as an oral drug, ribociclib can be delivered to patients more easily than intravenous therapy in both rural and urban settings. However, pERC noted that in provinces where oral and intravenous cancer drugs have different mechanisms of reimbursement, patients' accessibility to oral treatments can be limited and associated with co-payments and deductibles.

Factors Affecting Budget Impact and Adoption Feasibility
pERC identified the high cost of ribociclib, the anticipated volume of patients, and the additional health care resources required for monitoring and managing toxicities associated with the combination therapy as being key challenges for implementation. The Committee concluded that the budget impact and impact on existing health care resources are underestimated and would be substantial.

Drug Wastage Associated With Dose Modifications
pERC noted that patients may not receive the full protocol dose of ribociclib due to dose reductions, such as those reported in the MONALEESA-2 trial. pERC considered that each patient would be dispensed a given number of tablets each month and that some wastage would occur, as it is unlikely that tablets not taken due to dose reductions would be taken into consideration when the patient's next dispensation of medication occurs.

Ensure Capacity to Manage Toxicities With Ribociclib
Given the risks of toxicity with ribociclib and the anticipated volume of patients, pERC noted that jurisdictions should consider developing guidelines or processes as well as infrastructure such as clinic space to monitor and manage toxicity in patients who receive ribociclib.

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

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

Breast cancer remains the most common malignancy diagnosed in Canadian women, with a projected 26,300 new cases and 5,000 deaths in 2017. Approximately 75% of breast cancers over-express estrogen or progesterone hormone receptors or both. Advanced or metastatic breast cancer remains incurable, with a median life expectancy of two to three years, and is treated systemically with palliative intent — that is, to prolong life while improving or maintaining QoL. Endocrine-based therapy is often considered first-line palliative treatment in HR-positive, HER2-negative disease. Commonly used treatment options include selective estrogen receptor modulators (e.g., tamoxifen), aromatase inhibitors (e.g., anastrozole, letrozole, or exemestane), selective estrogen receptor degraders (e.g., fulvestrant), and, less commonly, progesterone agents (e.g., megestrol acetate). pERC agreed with the pCODR Clinical Guidance Panel (CGP) that most endocrine-sensitive breast cancers inevitably develop acquired resistance to hormone-based therapy and that there is a need for new and effective therapies for patients with advanced or metastatic breast cancer that improve survival, have more favourable toxicity profiles, and improve QoL.

pERC deliberated on the results of one randomized, placebo-controlled, phase III trial (MONALEESA-2), that evaluated the efficacy and safety of ribociclib in combination with letrozole compared with placebo plus letrozole as first-line treatment for post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer. pERC considered that the results for PFS, the primary outcome of the trial, were statistically significant and clinically meaningful in favour of ribociclib plus letrozole. In addition, tumour response outcomes, including overall response rates, were also statistically significant in favour of ribociclib. pERC noted that the results for OS (a secondary outcome) are not yet mature and that, when they do become available, they may be confounded by the wide choice of therapies that are available to patients upon progression. pERC agreed with the CGP that PFS is an established and well agreed-upon primary end point in the setting of advanced or metastatic breast cancer. Given that first-line endocrine therapies have shown PFS outcomes ranging from 5 to 15 months, a nine-month increase in median PFS of ribociclib plus letrozole over placebo plus letrozole is of clinical importance.

pERC deliberated on the toxicity profile of ribociclib in combination with letrozole and noted that there were more frequent toxicities compared with letrozole monotherapy, including neutropenia, nausea, diarrhea, alopecia, leukopenia, vomiting, anemia, increased alanine aminotransferase, and increased aspartate aminotransferase. While adverse events (AEs) requiring treatment interruptions and dose reductions were higher in the ribociclib-treated group, treatment discontinuation as a consequence was relatively rare. Most of the AEs were low grade; however, the Committee noted that grade 3 or grade 4 AEs occurred more frequently in the ribociclib-treated arm, most of which were attributable to neutropenia. pERC noted that to minimize the risk of a clinically meaningful prolongation of the QT interval, co-administration of medications that are known to potentially prolong the QT interval should be avoided. pERC discussed that patients receiving treatment with ribociclib would require substantially more health care resources to monitor and manage AEs (e.g., clinic visits, blood work, ECGs, and nursing and pharmacy time) compared against letrozole alone. Overall, pERC agreed with the CGP as well as with the registered clinicians providing input that although ribociclib has more toxicity than letrozole, AEs could be managed with adequate monitoring and dose adjustments in clinical practice.

pERC discussed the available patient-reported outcomes data from the MONALEESA-2 trial and noted that the QoL scores showed no clinically meaningful changes from baseline and no meaningful differences between treatment arms. pERC also noted that, given the toxicity profile of ribociclib plus letrozole, a significant improvement in QoL in this population with advanced or metastatic breast cancer would be unlikely. Overall, the Committee agreed that ribociclib plus letrozole maintains QoL in this patient population and that AEs of ribociclib combined with letrozole did not significantly impact overall QoL.

pERC concluded that there is a moderate net clinical benefit to ribociclib plus letrozole compared with letrozole monotherapy in the treatment of post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as an initial endocrine-based therapy. In making this conclusion, pERC considered the clinically meaningful results in PFS, a manageable but not insignificant toxicity

profile, no significant detriment in QoL, and a need for treatment options that improve survival and that have more favourable toxicity profiles. However, at present, there was no evidence of a survival benefit with ribociclib and letrozole compared to letrozole alone.

pERC deliberated upon patient advocacy group input and concluded that ribociclib aligns with patient values. pERC noted that, according to patients, advanced or metastatic breast cancer has a significant and debilitating impact (both physical and social) on patients' QoL, including bone pain, insomnia, fatigue, muscle weakness, shortness of breath, nausea, and loss of appetite. pERC considered that patients value having access to effective treatment options that control the disease, reduce disease symptoms, provide additional treatment choices, and will allow them to live with better QoL than if they were to receive traditional chemotherapy regimens with more significant toxicity profiles. pERC acknowledged that patients who had direct experience with ribociclib indicated that the ribociclib combination had helped to stabilize and control their disease and that AEs were minimal and tolerable. pERC noted that in the MONALEESA-2 trial, despite the worse toxicity profile of ribociclib plus letrozole compared with letrozole monotherapy, QoL was maintained and showed no significant difference between treatment arms. Respondents also commented on the ease of taking the drug orally at home and noted that they appreciated the reduced travel requirements for treatment with ribociclib. As a result, the Committee concluded that ribociclib plus letrozole aligned with patient values.

The Committee deliberated on input from one group of registered clinicians. pERC agreed with the clinicians providing input that there would be a high incidence and prevalent patient population, similar to the population considered by the pCODR review of palbociclib in combination with letrozole, for the treatment of post-menopausal women with estrogen receptor (ER)–positive, HER2-negative advanced breast cancer as initial endocrine-based therapy. Further, the registered clinicians noted that although ribociclib plus letrozole was more toxic than letrozole alone and was associated with asymptomatic neutropenia and elevated aspartate aminotransferase levels, ribociclib was considered to be well tolerated overall. Improving PFS was considered important, as it delays time until patients require subsequent treatment with chemotherapy.

pERC deliberated upon the cost-effectiveness of ribociclib plus letrozole and concluded that it is not cost-effective when compared with letrozole monotherapy in post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as an initial endocrine-based therapy. pERC noted that the submitter's base-case incremental cost-effectiveness ratio (ICER) was lower than the pCODR Economic Guidance Panel's (EGP's) lower and upper bound ICERs. The Committee noted that the majority of the inputs and assumptions selected for the comparison with letrozole monotherapy were reasonable, and the EGP was able to modify inputs and address limitations appropriately. pERC noted that the EGP made the following changes to the model to address some of its limitations:

- Removing the post-progression incremental survival benefit of ribociclib plus letrozole: The model assumed that survival gains in the pre-progression state translate into the post-progression state. However, due to the immaturity of the OS data and the CGP's opinion that there is no biologic plausibility of benefit beyond progression, the projected OS gain is associated with significant uncertainty. To remove this uncertainty, the EGP limited the duration of treatment effect until the end of trial follow-up, thereby eliminating the post-progression incremental survival benefit of ribociclib plus letrozole.
- Using lower utility values in the post-progression state: The CGP indicated that the utilities observed in the MONALEESA-2 trial were higher than expected in clinical practice. To explore lower utility values in the post-progression period, the EGP elected to use literature-based utilities in the upper bound of the reanalysis.

Additionally, the Committee discussed the fact that the costs of monitoring and managing toxicities associated with the combination therapy are likely underestimated in the economic model and would be substantially higher. Overall, pERC agreed with the EGP's reanalyses that addressed the limitations identified in the submitted economic model. Thus, pERC concluded that ribociclib plus letrozole was not cost-effective at the submitted price compared with letrozole monotherapy.

pERC noted that, to assess the comparative effectiveness of ribociclib plus letrozole to comparators other than the one (letrozole plus placebo) used in the MONALEESA-2 trial, the submitter provided indirect treatment comparisons (ITCs) to palbociclib plus letrozole, tamoxifen, and chemotherapy. pERC agreed with the CGP that given the limitations in the data and the methods used in the submitted ITCs, the lack of head-to-head randomized controlled trials (RCTs), and the lack of long-term data for OS, the comparative effectiveness and safety of ribociclib plus letrozole versus comparators other than letrozole monotherapy are highly uncertain. The Committee agreed with the EGP that the ITC outcomes were

subject to a high level of uncertainty and that, therefore, those estimates could not be used to inform credible ICER estimates.

pERC noted that, in the absence of more robust evidence, the choice between ribociclib plus letrozole and palbociclib plus letrozole will likely depend upon relative overall cost, treatment availability, patient values and preferences, and clinical factors such as tolerability to AEs. pERC also discussed that a comparison of ICER estimates used in this and the previous palbociclib plus letrozole recommendation, which was issued by pERC in 2016, would likely be biased due to differences in the model inputs, model structures, assumptions, and methods used. pERC emphasized that the patient populations used to inform the majority of the model inputs in this submission and the palbociclib plus letrozole recommendation came from different trials (MONALEESA-2 for ribociclib plus letrozole; PALOMA-2 for palbociclib plus letrozole) and that a cross-economic model comparison of ICER estimates would likely be confounded by unadjusted clinical and methodological differences in the trials. However, pERC felt that given similar efficacy and costing of these two regimens it is likely that the cost effectiveness in the real world would be fairly similar between ribociclib-letrozole and palbociclib–letrozole.

pERC considered the feasibility of implementing a reimbursement recommendation for ribociclib plus letrozole for the treatment of post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as an initial endocrine-based therapy. pERC identified the high cost of ribociclib, the large eligible patient population, and additional health care resources required for monitoring and managing toxicities associated with the combination therapy as being key challenges. pERC noted that ribociclib, a high-cost drug, is to be added to existing therapy (e.g., letrozole), and overall treatment costs could be expected to increase if it were reimbursed. pERC noted that the submitted budget impact assumes that the majority of the market share for ribociclib plus letrozole will come from palbociclib plus letrozole, which according to the CGP seems unlikely, as currently palbociclib plus letrozole is not publicly reimbursed in a number of provinces. Therefore, pERC noted that the predicted market share for ribociclib plus letrozole is likely underestimated. In addition, the number of eligible patients would likely be larger, as there would exist a short-term, time-limited need to offer ribociclib plus letrozole to patients currently receiving letrozole monotherapy for the treatment of post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer. pERC had significant concerns about the capacity of jurisdictions to implement ribociclib in combination with letrozole given the potentially large number of eligible patients and the resources (e.g., clinic visits, blood work, ECGs, and nursing and pharmacy time) required to monitor and manage toxicities while on the combination therapy. Additionally, the Committee noted that drug wastage associated with dose modifications had not been accounted for in the submitted budget impact. pERC noted that patients may not receive the full protocol dose of ribociclib due to dose reductions such as those reported in the MONALEESA-2 trial. pERC considered that each patient would be dispensed a given number of tablets each month and that some wastage would occur, as it is unlikely that tablets not taken due to dose reductions would be taken into consideration when the patient's next dispensation of medication occurs. The Committee agreed that the submitted budget impact is substantially underestimated and concluded that a significant reduction in the price of ribociclib would be required to decrease the budget impact. In addition, jurisdictions will need to consider the significant impacts on available resources, including clinician, nursing, and pharmacy staff, when considering the feasibility of adoption.

pERC discussed the Provincial Advisory Group's (PAG's) request for guidance on a number of clinical scenarios to assist with implementation.

- Input from the PAG indicated that various aromatase inhibitors are available for the initial treatment of HR-positive, HER2–negative metastatic breast cancer, including anastrozole, letrozole, and exemestane. pERC agreed that ribociclib should be used in combination with letrozole based on the available RCT evidence. However, the Committee felt that, in patients with intolerance to letrozole, it would be reasonable to use another aromatase inhibitor in combination with ribociclib if no disease progression had occurred during letrozole plus ribociclib.
- pERC noted that the MONALEESA-2 trial excluded the following patient subgroups: (1) patients who relapsed more than 12 months after completion of prior (neo)adjuvant treatment with any nonsteroidal aromatase inhibitor, (2) patients with active or uncontrolled metastases to the central nervous system, and (3) perimenopausal or premenopausal women who had chemically induced menopause. pERC noted that there was insufficient evidence presented to make an informed recommendation on the use of ribociclib plus letrozole in these three patient subgroups.

- pERC noted that generalizing the MONALEESA-2 trial results to male patients might be reasonable but as males were not included in the trial, direct evidence is lacking at this time. It is unlikely that there will be trials specifically designed for this small group of patients and there is no biological rationale to assume that outcomes of ribociclib plus letrozole therapy would be different between male and female patients with HR-positive, HER2-negative advanced or metastatic breast cancer.
- pERC noted that as an oral drug, ribociclib can be delivered to patients more easily than intravenous therapy in both rural and urban settings. However, pERC noted patient input indicating that in provinces where oral and intravenous cancer drugs have different mechanisms of reimbursement, accessibility to oral treatments can be limited and associated with co-payments and deductibles.
- pERC discussed the sequencing of treatments in HR-positive, HER2–negative advanced or metastatic breast cancer. Specifically, the Committee was unable to draw conclusions on the optimal sequencing of ribociclib plus letrozole with everolimus plus exemestane, as there is no evidence to date to inform this clinical situation. pERC agreed that, upon implementation of reimbursement of ribociclib plus letrozole, provinces should collaborate to develop national evidence-based clinical practice guidelines to inform this clinical situation.
- pERC noted that at the time of implementing a funding recommendation for ribociclib plus letrozole, jurisdictions may consider addressing the short-term, time-limited need to offer ribociclib plus letrozole to patients who are not resistant to (neo)adjuvant nonsteroidal aromatase inhibitor therapy and who recently started letrozole monotherapy for the treatment of post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as an initial endocrine-based therapy.

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
- guidance from the pCODR clinical and economic review panels
- input from two patient advocacy groups: Rethink Breast Cancer and Canadian Breast Cancer Network
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The objective of this review is to evaluate the effectiveness and safety of ribociclib (Kisqali) in combination with letrozole compared against standard endocrine therapy alone as first-line treatment in post-menopausal women with hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

Studies included: One randomized, placebo-controlled, phase III trial

The pCODR systematic review included one randomized, placebo-controlled, phase III trial: MONALEESA-2. The MONALEESA-2 trial evaluated the efficacy and safety of ribociclib in combination with letrozole compared with placebo plus letrozole as first-line treatment for post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer.

A total of 668 patients were randomized in MONALEESA-2, with 334 assigned to ribociclib plus letrozole and 334 to placebo plus letrozole. Patients in the experimental group were treated with oral ribociclib (600 mg per day on days 1 to 21 of a 28-day cycle) and letrozole (2.5 mg per day on a continuous schedule), and patients in the placebo group received letrozole at the same dose and schedule. All patients received treatment until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. Dose reductions were permitted for ribociclib but not for letrozole (in both treatment groups). To manage adverse events (AEs) associated with ribociclib, the dose could be reduced from 600 mg to 400 mg to 200 mg per day. Patients discontinuing treatment with either ribociclib or placebo could continue to receive letrozole; however, no treatment crossover was permitted.

The median time on treatment was comparable between the treatment groups: 13 months in the ribociclib plus letrozole group and 12.4 months in the placebo plus letrozole group. The median dose intensity was 100% for letrozole in both groups, and 100% and 87.5% for placebo and ribociclib, respectively.

Women enrolled were post-menopausal and had HR-positive, HER2-negative, locally advanced or metastatic breast cancer not amenable to curative treatment, with no previous systemic therapy for their advanced disease, and an ECOG performance status of 0 or 1. Randomization was 1:1 and stratified according to the presence or absence of liver and lung metastases.

Patient populations: Stage IV disease, ECOG performance status 0 to 1, median age 62 years

MONALEESA-2 included 668 post-menopausal women with advanced or metastatic breast cancer. Overall, the baseline characteristics of patients were well balanced between the two treatment groups. Most randomized patients were treated at trial sites in Europe (44.3%) and North America (34.3%), with fewer patients treated in Asia (10.2%). The median age was 62 years, with 44.2% of patients aged 65 and older. All patients had an ECOG performance status of 0 or 1 and had HR-positive disease, and all but two patients (one in each treatment group) were HER2-negative (99.7%). The majority of patients were white (82.2%), had stage IV disease (99.4%), and had a disease-free interval of ≥ 24 months (59.4%). Approximately one-third (34%) of patients had de novo advanced or metastatic breast cancer. The most common sites of metastases were bone (any, 73.4%; only, 22%) and visceral (58.8%; lung and/or liver only, 55.8%), and approximately one-third (34%) of patients had three or more metastatic sites. The

percentages of patients previously treated in the neoadjuvant or adjuvant setting with endocrine therapy and chemotherapy were 51.8% and 43.6%, respectively. All patients had prior surgery (including biopsy), and approximately half of patients (51.6%) had received prior radiotherapy.

Key efficacy results: Clinically meaningful progression-free survival

pERC deliberated on the key efficacy outcomes in the MONALEESA-2 trial. The primary outcome of the trial was progression-free survival (PFS) by local investigator assessment. Secondary outcomes included overall survival (OS), overall response rate, clinical benefit rate, health-related quality of life (QoL), and safety. Duration of response was an exploratory outcome. The trial met its primary outcome and demonstrated a statistically significant improvement in PFS by investigator assessment in the ribociclib plus letrozole treatment group after a median follow-up of 15.3 months; median PFS was not reached in the ribociclib plus letrozole group and was 14.7 months in the placebo plus letrozole group (hazard ratio 0.56; 95% confidence interval [CI], 0.43 to 0.72; $P = 3.29 \times 10^{-6}$). The updated analysis of PFS, which was based on an additional 11 months of follow-up, showed that the PFS benefit was sustained and that ribociclib plus letrozole improved PFS by 9.3 months over placebo plus letrozole (hazard ratio 0.57; 95% CI, 0.46 to 0.70; $P = 9.63 \times 10^{-8}$), with median PFS of 25.3 months (95% CI, 23.0 to 30.3) in the ribociclib plus letrozole group and 16 months (95% CI, 13.4 to 18.2) in the placebo plus letrozole group. pERC agreed with the pCODR Clinical Guidance Panel (CGP) that PFS is an established and well agreed-upon primary end point in the setting of advanced or metastatic breast cancer.

At interim and the second updated analysis, data on OS were immature. Median OS was not reached in the ribociclib plus letrozole group and was 33 months in the placebo plus letrozole group (hazard ratio 0.75; 95% CI, 0.52 to 1.08); this difference in OS between the groups still did not reach the threshold for statistical significance ($P = 0.059$). Clinical benefit rate, defined as the sum of complete and partial responses and stable disease for 24 weeks or more, was 79.9% and 73.1% (absolute difference of 6.8%; *P* value not reported) in the ribociclib plus letrozole group and placebo plus letrozole groups, respectively, at the second updated analysis. Data on duration of response, an exploratory end point of the trial, were reported for a subgroup of patients who had a confirmed complete or partial response. Median duration of response was 26.7 months (95% CI, 24.0 to not reached) in the ribociclib plus letrozole group and 18.6 months (95% CI, 14.8 to 23.1) in the placebo plus letrozole group.

Patient-reported outcomes: QoL was maintained, no difference between treatment arms

QoL outcomes were collected in MONALEESA-2. Patient-reported outcomes were evaluated using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 20 (QLQ-C30), version 3.0, along with the disease-specific breast cancer module (EORTC QLQ-BR23, version 1.0) and the EuroQoL 5-Dimensions instrument (EQ-5D-5L, version 4.0). The addition of ribociclib to letrozole did not appear to lead to an improvement or a detriment in health-related QoL. QoL scores showed no clinically meaningful changes from baseline and no meaningful differences between treatment arms. There was a slight improvement in scores for patients in both treatment arms during the treatment phase of the trial. Assessment of mean changes from baseline demonstrated no clinically meaningful differences between the treatment groups in the global health status and QoL scores at any time point (that is, no difference met the minimal clinically important difference threshold of ≥10 points). Results of the linear mixed regression model analysis showed no significant effect of treatment, time, or treatment by time interactions on the global health status and QoL scores; the estimated mean difference in changes in global health status and QoL scale scores between the treatment groups was −1.5 (95% CI, −4.0 to 1.0).

Safety: Toxicities requiring substantially more health care resources for monitoring

The safety analysis population included 334 patients in the ribociclib plus letrozole group and 330 patients in the placebo plus letrozole group. The majority of AEs in both treatment groups were low grade (grade 1 or 2).The most common AEs, of any grade, occurring more frequently in the ribociclib plus letrozole treatment group (versus placebo plus letrozole) included neutropenia (74.3% versus 5.2%), nausea (51.5% versus 28.5%), diarrhea (35% versus 22.1%), alopecia (33.2% versus 15.5%), leucopenia (32.9% versus 3.9%), vomiting (29.3% versus 15.5%), anemia (18.6% versus 4.5%), increased alanine aminotransferase (15.6% versus 3.9%), and increased aspartate aminotransferase (15% versus 3.6%). While AEs requiring treatment interruptions and dose reductions were higher in the ribociclib-treated group (versus placebo plus letrozole) — 68% (versus 13.3%) and 50.6% (versus 4.2%) — treatment discontinuation as a consequence was relatively rare, at 7.5% (versus 2.1%). The frequency of grade 3 or 4 AEs was higher in the ribociclib plus letrozole group (81.2%) compared with the placebo plus letrozole group (32.7%); the majority of higher grade events in the ribociclib group were attributable to neutropenia (59.3%).

There were 10 deaths during the treatment phase of the trial: seven (2.1%) in the ribociclib plus letrozole treatment group and three (0.9%) in the placebo plus letrozole group. This included a sudden death in the ribociclib plus letrozole group that occurred in association with grade 3 hypokalemia and a grade 2 prolongation in the QTcF interval (QT interval corrected for heart rate according to Fridericia's Formula) resulting from a prohibited concomitant medication with a known risk for QT prolongation. pERC noted that patients on ribociclib plus letrozole would require substantially more frequent clinic visits and health care resources to monitor for and treat AEs than would patients on letrozole monotherapy.

Comparator information: Palbociclib plus letrozole and other aromatase inhibitors

To assess the comparative efficacy and effectiveness of ribociclib plus letrozole to comparators other than the one (letrozole plus placebo) used in the MONALEESA-2 trial, the submitter provided an indirect treatment comparison (ITC) and a matching-adjusted indirect comparison (MAIC) of ribociclib plus letrozole and palbociclib plus letrozole and a network meta-analysis comparing ribociclib plus letrozole to endocrine-based therapies and chemotherapy for the first-line treatment of post-menopausal women with HR-positive and HER2-negative advanced or metastatic breast cancer. Limitations identified in the critical appraisal of the indirect comparisons included a substantial amount of missing data and variation of important baseline patient characteristics (treatment effect modifiers), a lack of adjustment for differences between trials in important treatment effect modifiers, and the inability to adjust for the influence of heterogeneity due to constraints in the structure of the evidence networks (e.g., single trial connections or small number of trials). pERC agreed with the CGP that given the lack of head-to-head randomized controlled trials (RCTs), the limitations in the ITCs, and the lack of long-term data for OS, the comparative effectiveness and safety of ribociclib plus letrozole versus comparators, other than letrozole monotherapy, is highly uncertain. pERC noted that given the lack of more robust evidence at this time, the choice between ribociclib plus letrozole versus palbociclib plus letrozole will likely depend upon relative overall cost, treatment availability, patient values and preferences, and clinical factors such as tolerability to AEs. However, pERC felt that given similar efficacy and costing of these two regimens it is likely that the cost effectiveness in the real world would be fairly similar between ribociclib-letrozole and palbociclib–letrozole.

Need and burden of illness: Need to delay disease progression, defer toxic chemotherapy

Breast cancer remains the most common malignancy diagnosed in Canadian women, with a projected 26,300 new cases and 5,000 deaths in 2017. Approximately 75% of breast cancers over-express estrogen or progesterone hormone receptors or both. Advanced or metastatic breast cancer remains incurable and is treated systemically with palliative intent. Commonly used options include selective estrogen receptor modulators (e.g., tamoxifen), aromatase inhibitors (e.g., anastrozole, letrozole, and exemestane), selective estrogen receptor degraders (e.g., fulvestrant), and, less commonly, progesterone agents (e.g., megestrol acetate). Patients will eventually progress and will have only the option of traditional chemotherapies, which have substantial toxicities. pERC considered that there is a need for new and effective therapies that delay disease progression, defer the need for toxic chemotherapy, and afford additional highly valued quality time to patients.

Registered clinician input: Large patient population, clinically important progression-free survival, more but manageable toxicities

The Committee deliberated on input from one clinician group. pERC agreed with the clinicians providing input that there would be a high incidence and prevalent patient population, similar to the population considered by the pCODR review of palbociclib in combination with letrozole, for the treatment of post-menopausal women with estrogen receptor (ER)-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy. Further, the clinicians noted that although ribociclib plus letrozole was more toxic than letrozole alone and was associated with asymptomatic neutropenia and elevated AST levels, ribociclib was considered to be well tolerated overall. Improving PFS was considered important, as it delays the time until patients require subsequent treatment with chemotherapy. According to the registered clinicians, premenopausal women with ovarian suppression would also be eligible for ribociclib.

PATIENT-BASED VALUES

Values of patients with advanced or metastatic breast cancer: Disease control, reduced symptoms, better toxicity than chemotherapy

pERC deliberated upon input from two patient advocacy groups and concluded that ribociclib aligns with patient values. From a patient's perspective, managing a diagnosis of metastatic breast cancer is challenging, as current treatment options for metastatic breast cancer are effective only at prolonging progression-free survival; most cases of advanced disease will progress and symptoms will worsen. Advanced or metastatic breast cancer has a significant and debilitating impact (both physical and social) on patients' quality of life. Patient input indicated that bone pain, insomnia, fatigue, muscle weakness, shortness of breath, nausea, and loss of appetite were the most common symptoms experienced as a result of breast cancer. Respondents indicated that ability to work, ability to perform household chores, ability to travel, and ability to pursue personal hobbies and interests were also impacted by the disease.

Respondents reported receiving a number of treatments, such as palbociclib, letrozole, capecitabine, paclitaxel, fulvestrant, and exemestane, among others. Patients value having access to effective treatment options that control the disease, reduce disease symptoms, provide additional treatment choices, and will allow them to live with better QoL than if they were to receive traditional chemotherapy regimens with more significant toxicity profiles.

Patient values on treatment: Disease control, minimal and tolerable side effects

Respondents who have experience with ribociclib reported that the treatment helped to stabilize and control their disease. Respondents also commented on the ease of taking the drug orally at home and appreciated the reduced travel requirements for treatment with ribociclib and that the side effects were minimal and tolerable.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility and cost-effectiveness analyses

The pCODR Economic Guidance Panel (EGP) assessed one cost-utility analysis (clinical effects measured by quality-adjusted life-years gained) and one cost-effectiveness analysis (clinical effects measured by life-years gained) of ribociclib in combination with letrozole compared with letrozole monotherapy for the treatment of post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer who received no prior therapy. To assess the comparative effectiveness of ribociclib plus letrozole to comparators other than the one (letrozole plus placebo) used in the MONALEESA-2 trial, the submitter provided ITCs to palbociclib plus letrozole, tamoxifen, and chemotherapy.

Basis of the economic model: Clinical and economic inputs

The key clinical outcomes considered in the cost-utility analysis were PFS and OS and utilities. Non-comparative data were used to inform the comparison of ribociclib plus letrozole against palbociclib plus letrozole, tamoxifen, and chemotherapy.

Costs considered in the analyses included drug acquisition, monitoring/management, AEs, subsequent therapy, and terminal care.

Drug costs: Treatment cost of ribociclib and comparators

Ribociclib costs $99.20 per 200 mg tablet. At the recommended dose of 600 mg daily for 21 days, 7 days off, ribociclib costs $223.21 per day and $6,249.99 per 28-day cycle.

Letrozole costs $1.37 per 2.5 mg tablet. At the recommended dose of 2.5 mg daily throughout the 28-day cycle, letrozole costs $1.37 per day and $38.58 per 28-day cycle.

Palbociclib costs $297.62 per 125 mg tablet. At the recommended dose of 125 mg daily for 21 days, 7 days off, palbociclib costs $223.22 per day and $6,250.02 per 28-day cycle.

Tamoxifen costs $0.35 per 20 mg tablet. At the recommended dose of 20 mg daily throughout the 28-day cycle, tamoxifen costs $0.35 per day and $9.80 per 28-day cycle.

Ribociclib plus letrozole treatment should continue until unacceptable toxicity or disease progression. The median time on treatment in the MONALEESA-2 trial was comparable between the treatment groups: 13 months in the ribociclib plus letrozole group and 12.4 months in the placebo plus letrozole group.

Cost-effectiveness estimates: Not cost-effective at submitted price

pERC deliberated upon the cost-effectiveness of ribociclib plus letrozole and concluded that it is not cost-effective when compared with letrozole monotherapy in post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as an initial endocrine-based therapy. pERC noted that in the submitted base case, the incremental cost-effectiveness ratio (ICER) was lower than the pCODR EGP's lower bound and upper bound ICER. The factors that most influence cost include the choice of comparator (letrozole monotherapy versus palbociclib plus letrozole), the parametric function for OS, and the dose intensity of ribociclib. The factors that most influence effectiveness include the choice of comparator, the parametric function for OS, and the duration of treatment effect. The EGP made the following changes to the model to address some of its limitations:

- Removing the post-progression incremental survival benefit of ribociclib plus letrozole: The model assumed that survival gains in the pre-progression state translated into the post-progression state. However, due to the immaturity of the OS data and the CGP's opinion that there is no biologic plausibility of benefit beyond progression, the projected OS gain is associated with uncertainty. To remove this uncertainty, the EGP set the treatment effect equal to 1.
- Using lower utility values in the post-progression state: The CGP indicated that the utilities observed in the MONALEESA-2 trial seemed high. To explore lower utility values in the post-progression period, the EGP elected to use literature-based utilities in the upper bound of the reanalysis.

Additionally, the Committee discussed the fact that the costs of monitoring and managing toxicities associated with the combination therapy are likely underestimated in the economic model and would be substantially higher. Overall, pERC agreed with the EGP's reanalyses and the limitations identified in the submitted economic model. pERC therefore accepted the EGP's estimates of the ICERs. pERC concluded that ribociclib plus letrozole was not cost-effective at the submitted price compared with letrozole monotherapy.

pERC agreed with the EGP's approach to not provide reanalysis estimates for the comparison of ribociclib plus letrozole versus palbociclib plus letrozole, tamoxifen, and chemotherapy, given limitations in the submitted ITCs. pERC agreed with the CGP that given the lack of head-to-head RCTs, the limitations in the ITCs, and the lack of long-term data for OS, the comparative effectiveness and safety of ribociclib plus letrozole versus comparators, other than letrozole monotherapy, is highly uncertain.

pERC further deliberated on the difference between the economic analyses and cost effectiveness of ribociclib plus letrozole and palbociclib plus letrozole and although it is difficult to compare across trials and different economic analyses, felt that, given similar effects observed in the respective trials and comparable drug acquisition costs, a substantial difference in the cost-effectiveness of those two therapies would be unlikely.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Large population, high drug cost, and substantial additional resources for monitoring and managing toxicities

pERC considered the feasibility of implementing a reimbursement recommendation for ribociclib plus letrozole for the treatment of post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as an initial endocrine-based therapy. pERC identified the high cost of ribociclib, the large eligible patient population, and additional health care resources required for monitoring and managing toxicities associated with the combination therapy as being key challenges. pERC noted that ribociclib, a high-cost drug, is to be added to existing therapy, and overall treatment costs could be expected to increase if it were reimbursed. pERC noted that the submitted budget impact assumes that the majority of the market share for ribociclib plus letrozole will come from palbociclib plus letrozole, which according to the CGP seems unlikely, as currently palbociclib plus letrozole is not publicly reimbursed in a number of provinces. Therefore, pERC noted that the predicted market share for ribociclib plus letrozole is likely underestimated. In addition, the number of eligible patients would likely be larger as there would exist a short-term, time-limited need to offer ribociclib plus letrozole to patients

currently receiving letrozole monotherapy for the treatment of post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer. pERC had significant concerns about the capacity of jurisdictions to implement ribociclib in combination with letrozole given the potentially large number of eligible patients and resources (i.e., clinic visits, blood work, electrocardiograms (ECGs), and nursing and pharmacy time) required to monitor and manage toxicities while on the combination therapy. Additionally, the Committee noted that drug wastage associated with dose modifications had not been accounted for in the submitted budget impact. pERC noted that ribociclib is delivered in packages of 200 mg tablets, which may reduce but not eliminate wastage occurring at dose adjustments or dose discontinuations. The Committee agreed that the submitted budget impact is substantially underestimated and concluded that a significant reduction in the price of ribociclib would be required to decrease the budget impact. In addition, jurisdictions will need to consider the significant impacts on available resources, clinic space, clinician, nursing, and pharmacy staff, when considering the feasibility of adoption.

pERC discussed the PAG's request for guidance on a number of clinical scenarios to assist with implementation.

- Input from the PAG indicated that various aromatase inhibitors are available for the initial treatment of HR-positive, HER2-negative metastatic breast cancer, including anastrozole, letrozole, and exemestane. pERC agreed that ribociclib should be used in combination with letrozole based on the available RCT evidence. However, the Committee felt that, in patients with intolerance to letrozole, it would be reasonable to use another aromatase inhibitor in combination with ribociclib if no disease progression had occurred during letrozole plus ribociclib.
- pERC noted that the MONALEESA-2 trial excluded the following patient subgroups: (1) patients who relapsed more than 12 months after completion of prior (neo)adjuvant treatment with any nonsteroidal aromatase inhibitor, (2) patients with active or uncontrolled metastases to the central nervous system, and (3) perimenopausal or premenopausal women who had chemically induced menopause. pERC noted that there was insufficient evidence presented to make an informed recommendation on the use of ribociclib plus letrozole in these three patient subgroups.
- pERC noted that generalizing the MONALEESA-2 trial results to male patients might be reasonable but as males were not included in the trial, direct evidence is lacking at this time. It is unlikely that there will be trials specifically designed for this small group of patients and there is no biological rationale to assume that outcomes of ribociclib plus letrozole therapy would be different between male and female patients with HR-positive, HER2-negative advanced or metastatic breast cancer.
- pERC noted that as an oral drug, ribociclib can be delivered to patients more easily than intravenous therapy in both rural and urban settings. However, pERC noted patient input indicating that in provinces where oral and intravenous cancer drugs have different mechanisms of reimbursement, accessibility to oral treatments can be limited and associated with co-payments and deductibles.
- pERC discussed the sequencing of treatments in HR-positive, HER2–negative advanced or metastatic breast cancer. Specifically, the Committee was unable to draw any conclusions on the optimal sequencing of ribociclib plus letrozole with everolimus plus exemestane, as there is no evidence to date to inform this clinical situation. pERC agreed that, upon implementation of reimbursement of ribociclib plus letrozole, provinces should collaborate to develop national evidence-based clinical practice guidelines to inform this clinical situation.
- pERC noted that at the time of implementing a funding recommendation for ribociclib plus letrozole, jurisdictions may consider addressing the short-term, time-limited need to offer ribociclib plus letrozole to patients who are not resistant to (neo)adjuvant aromatase inhibitor therapy and who recently started letrozole monotherapy for the treatment of post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as an initial endocrine-based therapy.

DRUG AND CONDITION INFORMATION

Drug Information	• Ribociclib is a selective cyclin-dependent kinase inhibitor • 200 mg film-coated tablet • Ribociclib is administered at a dose of 600 mg (3 × 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days. Ribociclib should be co-administered with letrozole 2.5 mg taken once daily throughout the 28-day cycle
Cancer Treated	• Hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer • Ribociclib as initial endocrine-based therapy
Burden of Illness	• Breast cancer is the most common malignancy diagnosed in Canadian women, with a projected 26,300 new cases and 5,000 deaths in 2017. Approximately 75% of breast cancers over-express estrogen or progesterone hormone receptors or both. Advanced or metastatic breast cancer remains incurable and is treated systemically with palliative intent
Current Standard Treatment	• Selective estrogen receptor modulators (e.g., tamoxifen), aromatase inhibitors (e.g., anastrozole, letrozole, or exemestane), selective estrogen receptor degraders (e.g., fulvestrant), and, less commonly, progesterone agents (e.g., megestrol acetate)
Limitations of Current Therapy	• Most endocrine-sensitive breast cancers inevitably develop acquired resistance to hormone-based therapy

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)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Christopher Longo, Economist
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

Dr. Catherine Moltzan chaired the meeting in her capacity as Vice-Chair of pERC. All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Craig Earle and Dr. Kelvin Chan, who were not present at the meeting
- Dr. Maureen Trudeau, who was excluded from chairing and voting due to a conflict of interest
- Dr. Anil Abraham Joy, who was excluded from deliberations and voting due to a conflict of interest
- Carole McMahon, who was excluded from voting due to a conflict of interest

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee 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 ribociclib for advanced or metastatic breast cancer, through their declarations, three 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 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 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

pCODR does not assume any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).

APPENDIX 1: pERC RESPONSES TO PAG IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendations
• PAG is seeking guidance on the appropriateness of adding ribociclib to letrozole for patients who are already on letrozole but have not yet progressed.	• pERC noted that at the time of implementing a funding recommendation for ribociclib plus letrozole, jurisdictions may consider addressing the short-term, time-limited need to offer ribociclib plus letrozole to patients who are not resistant to (neo)adjuvant nonsteroidal aromatase inhibitor (NSAI) therapy (i.e., disease-free for at least a year from the completion of prior adjuvant NSAI therapy), and who recently started letrozole monotherapy for the treatment of post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as an initial endocrine-based therapy.
• PAG is seeking guidance on the appropriateness of second-line ribociclib plus letrozole therapy for patients previously treated for metastatic disease with other aromatase inhibitors.	• The MONALEESA-2 trial studied the combination of ribociclib with letrozole in the first-line advanced/metastatic setting. pERC agreed with the Clinical Guidance Panel that currently there is insufficient evidence to make an informed recommendation on the use of the combination therapy in second-line metastatic therapy or in the (neo)adjuvant setting.
• PAG noted that the MONALEESA-2 trial excluded the following patient subgroups: (1) patients who relapsed < 12 months after completion of prior (neo)adjuvant treatment with any nonsteroidal aromatase inhibitor, (2) patients with active or uncontrolled metastases to the central nervous system, (3) perimenopausal or premenopausal women who had chemically induced menopause, and (4) male patients with HR-positive, HER2-negative advanced or metastatic breast cancer. PAG is seeking information on whether the MONALEESA-2 trial results are generalizable to any of these subgroups.	• pERC noted that there was insufficient evidence presented to make an informed recommendation on the use of ribociclib plus letrozole in (1) patients who relapsed < 12 months after completion of prior (neo)adjuvant treatment with any nonsteroidal aromatase inhibitor, (2) patients with active or uncontrolled metastases to the central nervous system, or (3) perimenopausal or premenopausal women who had chemically induced menopause. • pERC noted that generalizing the MONALEESA-2 trial results to male patients might be reasonable but as males were not included in the trial, direct evidence is lacking at this time. It is unlikely that there will be trials specifically designed for this small group of patients and there is no biological rationale to assume that outcomes of ribociclib plus letrozole therapy would be different between male and female patients with HR-positive, HER2-negative advanced or metastatic breast cancer.
• PAG noted that various aromatase inhibitors are available for the initial treatment of advanced or metastatic disease in HR-positive, HER2-negative breast cancer. These include anastrozole, exemestane, and letrozole. PAG is seeking information on ribociclib in combination with other aromatase inhibitors.	• pERC agreed that ribociclib should be used in combination with letrozole based on the available evidence from randomized controlled trials (RCTs). However, the Committee felt that, in patients with intolerance to letrozole, it would be reasonable to use another aromatase inhibitor in combination with ribociclib if no disease progression had occurred during letrozole plus ribociclib.

PAG Implementation Questions	pERC Recommendations
• 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 ribociclib compared with the use of chemotherapy after ribociclib.	• pERC was unable to make an informed recommendation on the optimal sequencing of ribociclib plus letrozole with everolimus plus exemestane, as the Committee noted that, as yet, there is no evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of ribociclib plus letrozole and noted that a national approach to developing evidence-based clinical practice guidelines would be of value.
• PAG noted that drug wastage may not be as much of an issue given one-tablet strength during dose adjustments.	• pERC noted that ribociclib is delivered in packages of 200 mg tablets, which may reduce but not eliminate wastage occurring at dose adjustments or discontinuations. pERC noted that patients may not receive the full protocol dose of ribociclib due to dose reductions, such as those reported in the MONALEESA-2 trial. pERC considered that each patient would be dispensed a given number of tables each month and that some wastage would occur, as it is unlikely that tablets not taken due to dose reductions would be taken into consideration when the patient's next dispensation of medication occurs.
• PAG noted the need for additional monitoring and treatment of toxicities, including the high incidence of neutropenia, and the risk of QT interval prolongation when on ribociclib plus letrozole.	• pERC had significant concerns about the capacity of jurisdictions to implement ribociclib in combination with letrozole given the potentially large number of patients eligible for ribociclib and the resources required to monitor and manage toxicities while on the combination therapy. Therefore, implementation of ribociclib plus letrozole could lead to significantly increased resource utilization (e.g., frequent clinic visits, blood work, electrocardiograms (ECGs), and associated nursing and pharmacy time).
• PAG noted that as an oral drug, ribociclib can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home.	• pERC noted that, as an oral drug, ribociclib can be delivered to patients more easily than intravenous therapy in both rural and urban settings. However, pERC noted that in provinces where oral and intravenous cancer drugs have different mechanisms of reimbursement, patients' accessibility to oral treatments can be limited and associated with co-payments and deductibles.
• PAG is seeking information on the comparison of ribociclib plus letrozole to palbociclib plus letrozole. • Is one combination better than the other? • Under what circumstances would ribociclib be preferred over palbociclib and vice versa? • Is switching possible between ribociclib and palbociclib, or vice versa (if intolerance)?	• pERC noted that, to assess the comparative effectiveness of ribociclib plus letrozole to palbociclib plus letrozole, the submitter provided indirect treatment comparisons (ITCs). pERC noted that, due to limitations in the data and the methods used to derive the estimates in the ITCs, the Economic Guidance Panel was unable to estimate credible incremental cost-effectiveness ratios. pERC noted that, at this time, the choice between ribociclib and palbociclib will likely depend upon relative overall cost, treatment availability, patient values and preferences, and clinical factors such as tolerability to adverse events. However, pERC felt that given similar efficacy and costing of these two regimens it is likely that the cost effectiveness in the real world would be fairly similar between ribociclib-letrozole and palbociclib-letrozole.