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: Ribociclib (KISQALI)

Submitted Reimbursement Request:
Ribociclib in combination with an aromatase inhibitor (AI) and a luteinizing hormone-releasing hormone (LHRH) agonist for the treatment of pre-/peri- menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer (ABC), as initial endocrine-based therapy.

Submitted By: Novartis Pharmaceuticals Canada Inc.	**Manufactured By:** Novartis Pharmaceuticals Canada Inc.
NOC Date: February 7, 2020	**Submission Date:** August 26, 2019
Initial Recommendation: April 2, 2020	**Final Recommendation:** June 4, 2020

Approximate per Patient Drug Costs, per Month (28 Days)	Ribociclib costs $0.42 per mg and $253.95 per day. At the recommended dose of 600 mg (three 200 mg tablets) taken orally once daily for days 1 to 21 of a 28-day cycle, ribociclib costs $5,332.95 per 28-day course. Cost of ribociclib plus letrozole and goserelin: • $678.01 per day • $5,794.21 per 28-day course. Cost of ribociclib plus anastrozole and goserelin: • $677.58 per day • $5,768.95 per 28-day course.

pERC RECOMMENDATION

☐ **Reimburse**

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

☐ **Do not reimburse**

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

pERC conditionally recommends reimbursement of ribociclib (Kisqali) in combination with a nonsteroidal AI (NSAI) and an LHRH agonist as initial endocrine-based therapy in patients with pre- or peri-menopausal HR-positive, HER2-negative advanced or metastatic breast cancer if the following conditions are met:

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

Eligible patients include pre- and peri-menopausal women who have not received prior endocrine treatment (ET) for ABC. Treatment should be continued until disease progression or unacceptable toxicity. Patients should have a good performance status, no active or uncontrolled metastases to the central nervous system and may have received prior (neo)adjuvant ET and one line of chemotherapy for ABC. Patients who have had prior (neo)adjuvant therapy should be disease-free for at least one year from the completion of prior AI therapy or may have relapsed on or after the completion of prior tamoxifen therapy.

pERC made this recommendation because it was satisfied that compared to NSAI alone, there is a net clinical benefit of ribociclib plus NSAI based

on statistically significant and clinically meaningful improvements in progression-free survival (PFS) and overall survival (OS), a manageable but not insignificant toxicity profile, and no apparent detriment in health-related quality of life (QoL).

pERC agreed that ribociclib plus NSAI aligns with patients' values of delaying disease progression and prolonging life while maintaining QoL, having a manageable side effect profile and avoiding chemotherapy. Patients value an oral treatment option although in some jurisdictions there may be concerns about cost to individual patients and to institutions that have to navigate alternative funding sources.

pERC concluded that, based on the sponsor's economic analysis and at the submitted price, ribociclib plus NSAI is not considered cost-effective compared to NSAI alone. pERC noted the cost-effectiveness results are highly uncertain due to the short-term follow-up of the MONALEESA-7 trial and therefore are largely dependent on the extrapolation of clinical benefit beyond the trial follow-up period. The comparative cost-effectiveness of ribociclib plus NSAI to other relevant cyclin-dependent kinase (CDK) 4/6-based comparators (i.e., palbociclib or abemaciclib with an AI or fulvestrant) could not be reliably estimated due to a lack of direct evidence and a lack of robust indirect treatment comparisons (ITCs).

pERC noted the large budget impact of adding ribociclib to NSAI, which is driven by the high drug cost, the number of potentially eligible patients, the increased market share of ribociclib, and the additional health care resources needed to manage adverse events (AEs) (e.g., more frequent clinic visits, blood work, electrocardiograms [ECGs], and nursing and pharmacy time). pERC had concerns that the submitted budget impact may be underestimated.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness and Decrease Budget Impact
Given that pERC was satisfied that there is a net clinical benefit of ribociclib plus NSAI, jurisdictions may want to consider pricing arrangements that would improve cost-effectiveness to an acceptable level. pERC noted that a reduction in the price of ribociclib would be required in order to improve its cost-effectiveness to an acceptable level and to decrease the predicted budget impact.

Ribociclib in Combination With AI
To be consistent with other funded CDK 4/6 inhibitors, pERC noted that it would be acceptable to reimburse ribociclib with any AI, instead of limiting reimbursement to letrozole and anastrozole. Therefore, at the time of implementing a reimbursement recommendation for ribociclib plus NSAI, jurisdictions may consider extending the reimbursement to ribociclib in combination with any AI. Ribociclib in combination with tamoxifen is not recommended due to effects on QT interval prolongation.

Time-Limited Need for Ribociclib Plus NSAI in Patients Currently Receiving NSAI Monotherapy
At the time of implementing a funding recommendation for ribociclib plus NSAI, jurisdictions may want to consider addressing the short-term, time-limited need to offer ribociclib to patients who are not resistant to (neo)adjuvant AI therapy and who recently initiated AI monotherapy for the treatment of HR-positive, HER2-negative, pre- and peri-menopausal ABC as initial endocrine-based therapy.

Sequencing of Ribociclib Plus NSAI
pERC concluded that the optimal sequencing of ribociclib plus NSAI in relation to other available therapies for the treatment of patients with HR-positive, HER2-negative ABC who are treatment naive for ABC is currently unknown. Therefore, pERC was unable to make an evidence-informed recommendation on the sequencing of ribociclib plus NSAI with other treatments. pERC noted that jurisdictions may want to consider developing a common approach to the treatment sequencing of all the available drugs in this setting.

Please note: Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

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

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

Breast cancer is the most commonly diagnosed malignancy in Canadian women, with an estimated 26,900 new cases and 5,000 deaths in 2019. ABC remains incurable and is treated systemically with palliative intent with a median life expectancy of approximately two to three years. The goals of palliative systemic therapy are to maintain or improve QoL, to slow further progression of disease, and to prolong survival. In the absence of rapidly progressive disease or visceral crisis, ET is usually considered first-line palliative treatment in HR-positive, HER2-negative disease, based on its efficacy and favourable toxicity profile. Commonly used options include selective estrogen receptor modulators (e.g., tamoxifen), AIs (e.g., anastrozole, letrozole, and exemestane), selective estrogen receptor degraders (e.g., fulvestrant), and the use of these treatments in combination with a CDK 4/6 inhibitor (e.g., palbociclib, ribociclib, and abemaciclib). Ovarian suppression with LHRH agonists may also be employed in conjunction with systemic ET for pre-menopausal women. For patients who are pre-menopausal, endocrine therapeutic options are more limited, as standard treatments such as AI, fulvestrant, and, until most recently, CDK 4/6 inhibitors were only indicated for post-menopausal women. All prior randomized controlled trials (RCTs) evaluating CDK 4/6 inhibitor combination therapies as first-line ET for ABC included women who were post-menopausal at the time of development of metastatic disease. Some jurisdictions are funding CDK inhibitor combinations for patients with chemically induced menopause. pERC agreed with the Clinical Guidance Panel (CGP) that the exclusion of pre-menopausal women from these trials resulted in an important unmet clinical need for this patient population as first-line treatment options were, until recently, limited to single-agent ET with or without ovarian suppression or cytotoxic chemotherapy.

pERC deliberated the results of one randomized, multi-centre, double-blind, placebo-controlled, phase III trial (MONALEESA-7) that evaluated the efficacy and safety of ribociclib in combination with ET (either tamoxifen or NSAI letrozole or anastrozole, with goserelin) compared with placebo plus ET as first-line treatment for pre- or peri-menopausal women with HR-positive, HER2-negative ABC. pERC noted that MONALEESA-7 is the only trial of CDK 4/6 inhibitors in ABC that has focused enrolment to pre- and peri-menopausal women. pERC discussed that the trial demonstrated statistically significant and clinically meaningful improvements in PFS, the primary outcome of the trial, and OS in favour of ribociclib plus ET. For both outcomes, the treatment effect was consistent across patient subgroups, including by type of ET (NSAI or tamoxifen) used, although small sample sizes limited the interpretation of the data in some subgroups. In addition, other secondary outcomes assessed in the trial, including objective response rate and time to chemotherapy, also favoured treatment with ribociclib plus ET, when compared to placebo plus ET.

pERC deliberated the toxicity profile of ribociclib plus ET (NSAI or tamoxifen) and noted there were more frequent AEs with combination treatment compared with ET alone, with the most common AE being neutropenia. In the MONALEESA-7 trial, grade 3 neutropenia occurred in 51% of patients treated with ribociclib compared to 3% of patients treated with ET alone; and grade 4 neutropenia occurred in 10% versus 1% of patients, respectively. QT prolongation also occurred more frequently in patients treated with ribociclib plus ET (10%) compared to ET alone (2%); however, the increase was highest among those patients receiving ribociclib combined with tamoxifen (16% versus 7%, respectively) compared to patients who received ribociclib plus NSAI (7% versus 0%, respectively). pERC discussed that due to effects on QT prolongation, tamoxifen was not recommended as an endocrine partner to ribociclib in the approved Health Canada indication nor in the submitted reimbursement request. pERC noted that there were no serious AEs that occurred in more than 2% of patients in either treatment group. Treatment interruptions and dose reductions were higher in patients treated with ribociclib; however, treatment discontinuation due to AEs occurred in a relatively low percentage of patients (4% versus 3% with ET alone). Overall, pERC concluded that compared with NSAI alone, ribociclib plus NSAI had a manageable, but not insignificant, toxicity profile.

pERC discussed the health-related QoL data from the MONALEESA-7 trial, which focused on the time-to-10% deterioration in the European Organization for Research and Treatment of Cancer Quality of Life

Questionnaire-C30 (EORTC-QLQ-C30) and EuroQoL 5-Dimension 5-Level (EQ-5D-5L) scales compared to baseline scores, with the global health status and QoL scale being the primary patient-reported outcome of interest. The available data suggest that global health status and QoL and other scales (emotional functioning, EQ-5D Visual Analogue Scale [VAS]) favoured treatment with ribociclib plus ET or showed no difference between the treatment groups (physical functioning, breast symptoms) with respect to time-to-10% deterioration from baseline scores. pERC acknowledged, however, that the QoL results from the MONALEESA-7 trial may not accurately represent the QoL of patients treated with ribociclib plus ET as selection and confounding bias were raised by the pCODR Methods Team as limitations to the assessment of this outcome due to the proportion of patients that was lost to follow-up in the trial, and considering the greater frequency of AEs that occur when ribociclib is added to ET.

Based on evidence from the MONALEESA-7 trial, pERC concluded that compared to NSAI alone, there is a net clinical benefit to ribociclib plus NSAI as initial ET for pre- and peri-menopausal HR-positive, HER2-negative ABC. In reaching this conclusion, pERC considered the statistically significant and clinically meaningful improvements in PFS and OS, the manageable but not insignificant toxicity profile, that there is no apparent detriment in QoL outcomes, and the need for more first-line treatment options for women with pre- and peri-menopausal ABC.

In addition to the MONALEESA-7 trial, pERC also deliberated an ITC that was conducted by the sponsor to inform the pharmacoeconomic model supporting the reimbursement request. The ITC compared the relative efficacy (PFS) and safety of available treatments for HR-positive, HER2-negative ABC including CDK 4/6 inhibitors (palbociclib, abemaciclib) combined with AI and fulvestrant as relevant comparators. The ITC included nine trials; however, there were no trials of CDK 4/6 inhibitors whose populations mirrored that of the MONALEESA-7 trial. The only available comparisons were based on patient subgroup data from two trials, and these suggested no clear differences in PFS efficacy between ribociclib and other CDK 4/6 inhibitors in this population. The analysis of safety was based on a naive comparison of the incidence of grade 3 and 4 AEs across trials, which suggested CDK inhibitors, as a group, appear to carry a higher risk of various cytopenias, including neutropenia, when compared to other therapies. Clinical heterogeneity among the included trials was cited as a major limitation of the ITC. pERC agreed with the pCODR Methods Team that the ITC results should be interpreted with caution given the significant heterogeneity across the trials that could impact their comparability to the MONALEESA-7 trial and produce biased estimates of relative treatment effect.

pERC discussed the patient input received from two patient advocacy groups, Rethink Breast Cancer and Canadian Breast Cancer Network (CBCN) and agreed that ribociclib plus NSAI aligns with patient values, which include delaying disease progression, prolonging life while maintaining QoL, avoiding chemotherapy, and having a manageable side effect profile. pERC noted that a high proportion of surveyed patients cited the cost of prescription medications as having significant or some impact on their treatment decision-making and QoL. pERC had concerns that given their younger age, patients who are pre- and peri-menopausal without private insurance may not qualify for public drug plans and will have to pay out of pocket or rely on their treating physician or institution to navigate alternative funding sources to cover costs of treatment.

pERC deliberated the cost-effectiveness of ribociclib plus NSAI and goserelin compared to NSAI plus goserelin as initial ET for pre- and peri-menopausal ABC. pERC discussed the key limitations of the submitted economic model identified by the Economic Guidance Panel (EGP), which included the high uncertainty related to the long-term extrapolation of clinical benefit for ribociclib plus NSAI and goserelin based on short trial follow-up (45 months) and the fact that the median OS had not been reached for the ribociclib group, concerns on the method used to derive patients' transition probabilities that may inflate the impact of ribociclib on life expectancy and quality-adjusted life-years (QALYs), and inappropriate assumptions regarding end-of-life terminal care costs for ABC. These limitations made it challenging to reliably estimate the incremental treatment effect of ribociclib plus NSAI and goserelin. pERC noted that modifications to the submitted pharmacoeconomic model made by the EGP in reanalyses to address these limitations showed the incremental cost-utility ratio (ICUR) was highly sensitive to shortening the time horizon to 10 years, variation in the parametric models used to predict long-term PFS data, and applying the same transition probability from PFS to death for all treatments. Compared to the sponsor's submitted base-case ICUR, these changes resulted in a higher ICUR for the EGP's best-case estimate and a wide range for the lower and upper bound of the estimate. pERC therefore concluded that compared to NSAI plus goserelin, ribociclib plus NSAI and goserelin was not cost-effective at the submitted price. pERC considered that given that drug price was a key driver of the incremental cost-effectiveness estimates, a reduction in drug price would be required to improve cost-effectiveness to an acceptable level. pERC noted that more mature OS data from MONALEESA-7 would help to decrease the uncertainty in the incremental treatment effect and inform on a more accurate estimate of the cost-effectiveness of

ribociclib plus NSAI and goserelin. The submitted model also included cost-effectiveness estimates for ribociclib plus NSAI plus goserelin compared to other relevant CDK 4/6-based therapies (i.e., palbociclib or abemaciclib with an AI or fulvestrant). pERC agreed with the EGP, however, that these estimates should be interpreted with caution due to the significant clinical heterogeneity of the included trials in the ITC. Therefore, pERC concluded that the comparative cost-effectiveness of ribociclib plus NSAI and goserelin to other relevant CDK 4/6-based comparators could not be reliably estimated due to a lack of direct evidence and lack of a robust ITC. pERC noted that, in the absence of such evidence, the choice between CDK 4/6 inhibitor-based therapies will likely depend on multiple factors that include relative overall cost, treatment funding availability in jurisdictions, patient values and preferences, and clinical factors such as tolerability to AEs.

pERC considered the feasibility of implementing a reimbursement recommendation for ribociclib plus NSAI and goserelin for the treatment of pre- and peri-menopausal women with HR-positive, HER2-negative ABC as initial ET. pERC discussed the factors that most influence the budget impact analysis (BIA), which include medication costs, the large eligible patient population, and the market share of ribociclib. pERC noted that ribociclib is to be added to existing therapy (e.g., single-agent ET); therefore, overall treatment costs would be expected to increase if the combination were reimbursed due to the high drug cost and the need for additional health care resources required for monitoring and managing the toxicities associated with the combination therapy. pERC commented that EGP reanalyses indicated the submitted BIA may be underestimated by not including drug wastage and if the relative dose intensity (RDI) of ribociclib is 100% in clinical practice. Further, given the limited sources for public funding in some provinces and territories, pERC felt the submitted BIA could be underestimated based on the proportion of patients that was estimated to have public coverage. pERC concluded that a reduction in the price of ribociclib would be required to decrease the predicted budget impact.

pERC also deliberated the input received from PAG regarding factors related to currently funded treatments, the eligible patient population, implementation factors, and sequencing of available treatments. Refer to the summary table in Appendix 1 for more details.

Upon reconsideration, pERC discussed the feedback received from stakeholder groups (the sponsor, one patient group, and PAG) regarding suggested clarifications to the eligible patient population. The sponsor and Rethink Breast Cancer both requested that pERC consider revising the initial recommendation to clarify that eligible patients could not have received prior ET for ABC, but they could have received one prior line of chemotherapy for ABC, as per the MONALEESA-7 trial eligibility criteria. pERC noted that 14% of patients in the MONALEESA-7 trial population (14% of patients in each treatment group) had received one prior line of chemotherapy. pERC agreed with the stakeholder feedback and revised the recommendation to clarify eligibility requirements regarding prior ET and chemotherapy for ABC. PAG requested that pERC consider adding and defining lack of resistance to prior (neo)adjuvant AI to the recommendation, which was listed as an eligibility requirement under Potential Next Steps for Stakeholders considering the time limited need for offering ribociclib to patients currently on NSAI monotherapy. Specifically, patients should be disease-free for at least one year from the completion of prior NSAI therapy to be considered for ribociclib. pERC discussed that unlike previous trials of CDK 4/6 inhibitor combination therapies as first-line ET for ABC, in MONALEESA-7, there was a choice of ET for ABC (NSAI or tamoxifen). The type of ET for ABC selected for patients in the trial depended on the type of prior (neo)adjuvant ET and the disease-free interval from (neo)adjuvant ET. pERC agreed that the recommendation should align with the trial criteria and therefore revised the recommendation to clarify eligibility requirements regarding prior neo(adjuvant) ET; specifically, patients who have had prior (neo)adjuvant therapy should be disease-free for at least one year from the completion of prior AI therapy or may have relapsed on or after the completion of prior tamoxifen therapy. Finally, PAG also requested that pERC consider including a statement under Potential Next Steps for Stakeholders to indicate that the sequencing of ribociclib plus NSAI with other available first-line therapies for ABC is unclear as it is unknown whether the clinical benefit of everolimus plus exemestane is maintained in the context of prior CDK 4/6 exposure. pERC agreed there is a lack of evidence on the sequencing of available treatments for patients who are treatment-naive for ABC and agreed such a statement was appropriate and consistent with other recommendations in this setting; therefore, a statement on sequencing was added under Potential Next steps for Stakeholders.

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 sponsor's economic model and BIA
- guidance from the pCODR clinical and economic review panels
- input from two patient advocacy groups (CBCN and Rethink Breast Cancer)
- input from registered clinicians: two clinicians on behalf of Cancer Care Ontario (CCO) Breast Drug Advisory Committee (DAC)
- 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 registered clinician group (CCO Breast DAC)
- PAG
- the sponsor (Novartis Pharmaceuticals Canada)

The pERC Initial Recommendation was to conditionally recommend reimbursement of ribociclib in combination with a NSAI and an LHRH agonist as initial endocrine-based therapy in patients with pre- or peri-menopausal HR-positive, HER2-negative ABC if the following conditions are met:

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

Feedback on the pERC Initial Recommendation indicated that one patient advocacy group (CBCN), the registered clinician group, and PAG agreed with the Initial Recommendation, and one patient advocacy group (Rethink Breast Cancer) and the sponsor agreed in part with the recommendation. All stakeholders supported conversion to a final recommendation. The pERC chair and pERC members reviewed the feedback received from stakeholders (Rethink Breast Cancer, the PAG, and the sponsor) and determined that clarifications related to the eligible patient population required reconsideration by pERC.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of ribociclib (Kisqali) in combination with an AI and an LHRH agonist as initial ET for pre- and peri-menopausal women with HR-positive, HER2-negative ABC.

Studies included: One multi-centre, double-blind, placebo-controlled phase III RCT (MONALEESA-7) was the focus of deliberation

The pCODR systematic review included one multi-centre, double-blind, phase III RCT. MONALEESA-7 is an ongoing, placebo-controlled superiority trial conducted in 188 sites in 30 countries. The trial enrolled 24 patients across six Canadian sites. The objective of the MONALEESA-7 trial was to assess the efficacy and safety of ribociclib in combination with ET in pre- and peri-menopausal women with HR-positive, HER2-negative ABC.

Eligible patients were randomized 1:1 to receive ribociclib at a dose of 600 mg orally once daily for days 1 to 21 of a 28-day cycle plus ET consisting of either tamoxifen (20 mg orally once daily) or an NSAI (letrozole 2.5 mg orally once daily or anastrozole 1 mg orally once daily) and goserelin (3.5 mg by subcutaneous implant on day one of the 28-day schedule), or placebo plus tamoxifen or NSAI and goserelin at the same doses and schedules. Treatment continued until there was disease progression, unacceptable toxicity, death or discontinuation for any reason. Patients were stratified based on the presence of lung or liver metastases, prior chemotherapy for advanced disease, and endocrine combination partner (tamoxifen or NSAI). Dose reductions were allowed for patients treated with ribociclib experiencing AEs (two levels, first to 400 mg, then to 200 mg) but were not permitted for

tamoxifen, NSAI, or goserelin. Patients discontinuing treatment with either ribociclib or placebo could continue to receive ET; however, no treatment crossover was permitted.

At the time of the primary efficacy analysis the median duration of treatment exposure was longer in the ribociclib treatment group at 15.2 months compared to 12.0 months in the placebo group; and the median RDI was 94% and 100%, respectively.

The pCODR review also included a summary and critical appraisal of the sponsor-submitted ITC. The sponsor conducted an ITC because the MONALEESA-7 trial did not provide a comparison to an active relevant treatment comparator. The sponsor-submitted ITC estimated the relative efficacy (PFS) and safety of ribociclib plus an NSAI compared to selected treatments for pre- and peri-menopausal women with HR-positive, HER2-negative ABC who have not received prior therapy for advanced disease. The ITC provided input for the pharmacoeconomic model in order to evaluate the cost-effectiveness and budget impact of ribociclib plus an NSAI for the indication under review.

Patient populations: Pre- and peri-menopausal women with metastatic disease, median age 43 to 45 years, and Eastern Cooperative Oncology Group performance status of 0

The MONALEESA-7 trial enrolled 672 pre- and peri-menopausal women with ABC. Overall, the baseline characteristics of patients were well balanced between the trial treatment groups. Enrolled patients had a median age of 43 and 45 years in the ribociclib and placebo groups, respectively. The most common sites of metastasis were the bone (74% of patients), visceral (57%) and lymph nodes (45%). Approximately 74% of patients had an Eastern Cooperative Oncology Group performance status of 0. Non-de novo patients made up 60% of the trial population, and of these patients, 54% had a disease-free interval of more than 12 months from initial diagnosis. Patients who had received (neo)adjuvant ET were eligible to receive either NSAI plus goserelin or tamoxifen plus goserelin for ABC in the trial if 12 or more months had elapsed since the last dose of (neo)adjuvant therapy; or, if tamoxifen was the last prior (neo)adjuvant therapy and the last dose was given within the last 12 months prior to randomization, then the patient was eligible to receive a NSAI plus goserelin for ABC; or, if letrozole, anastrozole, fulvestrant, or exemestane were the last prior therapy and the last dose was given within the last 12 months prior to randomization, then the patient was eligible to receive tamoxifen plus goserelin for ABC. Approximately 40% of trial patients had (neo)adjuvant ET, with 30% having progressed 12 months or fewer after ET and approximately 9% having progressed more than 12 months after ET (for 1% of patients these data were missing). There were 14% of trial patients who had received prior chemotherapy for ABC. Patients excluded from the trial included those who had received prior ET for ABC (with the exception that patients could have received ≤ 14 days of tamoxifen or an NSAI with or without goserelin, or only goserelin for 28 days or fewer for ABC prior to randomization), symptomatic visceral disease, central nervous system metastases, clinically significant uncontrolled heart disease or cardiac repolarization abnormality, inflammatory breast cancer, and prior receipt of a CDK 4/6 inhibitor.

Key efficacy results: Statistically significant and clinically meaningful improvements in PFS and OS

The key efficacy outcomes deliberated on by pERC included PFS (investigator-assessed) and OS. Other secondary efficacy outcomes assessed in the MONALEESA-7 trial included tumour response outcomes (objective response rate, duration of response, time to response) and time to chemotherapy; the results for these outcomes were consistent with the PFS and OS results.

At the data cut-off for the primary efficacy analysis (August 20, 2017), the median follow-up time of patients was 19.2 months. At this time, there were 318 progression events across the trial, and fewer progression events in the ribociclib plus ET group (n = 131; 39% of patients) versus the placebo plus ET group (n = 187; 56% of patients) for a statistically significant difference between groups (hazard ratio [HR] = 0.55; 95% confidence interval [CI]: 0.44 to 0.69; P < 0.0001). The median PFS in the ribociclib plus ET group was 23.8 months (95% CI, 19.2 to not reached) and was 13.0 months (95% CI, 11.0 to 16.4) in the placebo plus ET group. With respect to subgroup analyses, the treatment effect generally remained consistent across patient subgroups, although the small sample size in some groups limit interpretation. The PFS treatment effect estimates for patients who received an NSAI or tamoxifen were 0.57 (95% CI, 0.44 to 0.74) and 0.59 (95% CI, 0.39 to 0.88), respectively. The updated analysis of PFS (November 30, 2018) based on a median follow-up time of 34.6 months showed that the PFS benefit was sustained; the median PFS was 27.5 months in the ribociclib plus ET group and 13.8 months (CI not reported) in the placebo plus ET group, and the updated HR was 0.58 (95% CI, 0.48 to 0.70).

OS was a key secondary outcome that was assessed at three interim analyses that were triggered by the total number of deaths. There was no statistically significant difference in OS as of the date of the

primary efficacy analysis of PFS, with 13% (n = 43) of patients in the ribociclib group and 14% (n = 46) of patients in the placebo group with an event of death. However, by the time of the pre-planned second interim analysis, after a median follow-up of 34.6 months, there was a total of 192 deaths, with 25% (n = 83) of patients in the ribociclib group and 32% (n = 109) of patients in the placebo group with an event of death (HR = 0.71 [95% CI, 0.54 to 0.95]; P = 0.00973). This was deemed to be a statistically significant reduction in the risk of death with ribociclib plus ET versus placebo plus ET, as the P value crossed the pre-specified O'Brien-Fleming stopping boundary of P < 0.01018. A pre-specified analysis of OS based on endocrine partner was performed. In those receiving an NSAI, 25% (n = 61) of patients in the ribociclib group and 32% (n=80) of patients in the placebo group had died; while for those receiving tamoxifen, results were similar with 25% (n = 22) of patients receiving ribociclib and 32% (n = 29) of patients receiving placebo had died. The HR for death in those receiving an NSAI was 0.70 (95% CI, 0.50 to 0.98) and for those receiving tamoxifen was 0.79 (95% CI, 0.45 to 1.38).

Patient-reported outcomes: No deterioration in QoL

Patient-reported outcomes were evaluated in the MONALEESA-7 trial using the EORTC-QLQ-C30, the QLQ-BR23 (breast symptoms), and the EQ-5D-5L VAS. Health-related QoL was an exploratory outcome of the trial and the primary patient-reported variable of interest was the time-to-10% deterioration in the global health status and QoL scale of the EORTC-QLQ-C30. No minimal clinical important difference was specified for any of the health-related QoL assessment instruments. A 10% deterioration in any of the scales assessed was defined as a worsening in score by 10% or more when compared to baseline, with no later improvement above this threshold during the treatment period, or death due to any cause. Most patients (99%) had completed baseline assessments; however, end-of-treatment assessments were only completed for a proportion of the trial population (39% of patients in the ribociclib group and 53% in the placebo group). Although no formal statistical analyses were planned, the HR for time to deterioration in global health status and QoL was 0.70 (95% CI, 0.53 to 0.92), which suggests that overall HRQOL is not worse with ribociclib plus ET when compared to placebo plus ET. The other scales assessed appeared to favour treatment with ribociclib (emotional functioning; EQ-5D-5L VAS) or indicated no difference between treatment groups (physical functioning, breast symptoms).

Limitations: Lack of robust indirect comparisons to relevant CDK 4/6-based therapies

The sponsor submitted an ITC to compare ribociclib plus NSAI to other treatments for pre- and peri-menopausal women with HR-positive, HER2-negative ABC, based on data from MONALEESA-7 and other trials in order to inform the pharmacoeconomic model supporting the reimbursement request. Eligible trials were identified from a systematic review of electronic databases performed in April 2018 seeking RCTs and was supplemented with studies identified through a more targeted review of the literature. The ITC of PFS was conducted using the Bucher method, while AEs were evaluated using an unanchored (naive) comparison. After a request from pCODR, the ITC was updated to include other CDK 4/6 inhibitors combined with AI or fulvestrant as relevant comparators. The ITC included nine trials; however, there were no trials of CDK 4/6 inhibitors whose populations mirrored that of the MONALEESA-7 trial. The only available comparisons were based on patient subgroup data from two trials, and these suggested no clear differences in efficacy between ribociclib and other CDK 4/6 inhibitors in this population. The ITC results indicated that there was improved efficacy for ribociclib combined with an NSAI, when compared with palbociclib plus fulvestrant (HR = 0.69; 95% CI, 0.37 to 1.29) or abemaciclib plus fulvestrant (HR = 0.57; 95% CI, 0.31 to 1.04); however, these differences were not statistically significant. The pCODR Methods Team considered the significant heterogeneity in patient populations among the included trials as a major limitation of the ITC; there were notable differences across the trials related to menopausal status, endocrine partner, disease-free interval, inclusion of patients with de novo ABC, and line of therapy, as well as missing information on other important patient and trial characteristics (patient demographics, study locations, PFS definitions and assessment schedule, median follow-up time). Overall, the ITC results should be interpreted with caution given the significant clinical heterogeneity across trials that could impact their comparability to the MONALEESA-7 trial and produce biased estimates of relative treatment effect.

Safety: Increased toxicity compared to ET alone, notable harms include neutropenia and QT prolongation

AEs of any grade occurred in 98% and 94% of patients in the ribociclib plus ET group and placebo plus ET group, respectively. Grade 3 and 4 events occurred in 63% and 14% of patients treated with ribociclib, respectively, and 26% and 4%, respectively, in patients who received placebo. The most common AEs in the ribociclib plus ET group was neutropenia; grade 3 neutropenia occurred in 51% of patients treated with ribociclib versus 3% of patients who received placebo. Grade 4 neutropenia occurred in 10% versus 1%

of patients in the ribociclib group and placebo groups, respectively. However, febrile neutropenia rates were similar and occurred in 2% and 1% of patients treated with ribociclib and placebo, respectively. QT prolongation was another notable harm; QTcF increases of more than 60 ms occurred in 10% of patients treated with ribociclib compared to 2% of patients treated in the placebo group. QTcF increases of more than 60 ms were more common in the ribociclib group among patients receiving tamoxifen, where 16% of patients receiving ribociclib and 7% of those receiving placebo had increases in QTcF of more than 60 ms. Among patients receiving an NSAI, 7% of ribociclib patients in the ribociclib group versus no patients in the placebo group experienced an increase in QTcF of more than 60 ms. There were no cases of torsades de pointes in the trial. Serious AEs were reported in 18% of patients in the ribociclib group compared to 12% in the placebo group, and there were no serious AEs that occurred in more than 2% of patients in either group. There were two deaths in the ribociclib group that were deemed unrelated to the study treatment: one patient died of an intracranial hemorrhage and one patient died of wound hemorrhage.

Dose interruptions occurred in 77% of patients who received ribociclib and in 38% of patients who received placebo. Dose reductions occurred in 35% of patients who received ribociclib and 6% of patients who received placebo, most commonly for AEs in 31% and 5% of patients, respectively. Withdrawals due to AEs occurred in 4% and 3% of patients treated with ribociclib and placebo, respectively. The most common reason for a withdrawal due to an AE that was suspected to be related to drug therapy was increased alanine aminotransferase, which occurred in 2% of patients in the ribociclib group and none of the patients in the placebo group. An updated analysis of harms data based on longer follow-up showed that AEs were consistent with the primary analysis.

Need and burden of illness: Need for additional first-line treatments for pre- and peri-menopausal women with ABC

Breast cancer is the most commonly diagnosed malignancy in Canadian women, with an estimated 26,300 new cases and 5,000 deaths in 2019. Even among those cured from early-stage breast cancer, all will continue to have some risk of developing metastatic disease despite multimodality adjuvant therapy (e.g., chemotherapy, ET, radiation, and targeted therapy). It is estimated that, in Canada, approximately 5% to 10% of women present with de novo metastatic breast cancer. ABC remains incurable and is treated systemically with palliative intent with a median life expectancy of approximately two to three years. In the absence of rapidly progressive disease or visceral crisis, ET therapy is usually considered first-line palliative treatment in HR-positive, HER2-negative disease, based on its efficacy and favourable toxicity profile. Commonly used options include selective estrogen receptor modulators (e.g., tamoxifen), AI (e.g., anastrozole, letrozole, and exemestane), selective estrogen receptor degraders (e.g., fulvestrant), and, less commonly, progesterone agents (e.g., megestrol acetate). AI and fulvestrant are only appropriate for patients who are post-menopausal, whereas tamoxifen is effective regardless of menopausal status. Ovarian suppression with LHRH agonists may also be used in conjunction with systemic ET for pre-menopausal women. Unfortunately, all endocrine-sensitive breast cancers inevitably develop acquired resistance to ET, necessitating a change in systemic treatment. Additionally, a small proportion of patients with HR-positive disease at initial presentation do not respond to first-line ET, and are considered to have primary endocrine resistance. For patients who are pre-menopausal, endocrine therapeutic options are more limited as standard options such as AIs, fulvestrant, and, until most recently, CDK 4/6 inhibitors, were only indicated for post-menopausal women given that all prior RCTs evaluating CDK 4/6 inhibitors as initial ET for ABC enrolled women who were post-menopausal at the time of development of metastatic disease.

Registered clinician input: Preference for ribociclib plus AI over other treatments, acceptable toxicity profile

One joint submission was received that included input from two clinicians on behalf of CCO on the use of ribociclib in combination with an AI and an LHRH agonist for the treatment of pre- and peri-menopausal women with HR-positive, HER2-negative ABC as initial ET. Current therapies for the indication under review include various AIs such as anastrozole, exemestane, and letrozole. Based on the results of the MONALEESA-7 trial, the clinicians noted that the ribociclib combination with an AI and an LHRH agonist is superior to ET alone and exhibits an acceptable toxicity profile; thus, the CCO clinicians expect the treatment combination to be widely used in clinical practice. Despite availability of other ET options for pre- and peri-menopausal women with HR-positive, HER2-negative ABC, the CCO clinicians indicated they would administer the ribociclib plus AI combination in the first-line setting over abemaciclib, palbociclib, and ribociclib plus fulvestrant based on the clinical trial evidence. The CCO clinicians felt that there is limited evidence to extend the use of ribociclib plus AI to HER2-positive patients but would consider administering ribociclib plus an AI and LHRH agonist in male breast cancer patients. The clinicians cited

that ribociclib is contraindicated in patients with hypersensitivity to the drug or composite ingredients in the formulation and in patients with or at risk of pathological prolongation of the QT interval.

PATIENT-BASED VALUES

Experience of patients with HR-positive, HER2-negative ABC: Fatigue and pain symptoms impact QoL, financial concerns affect QoL and treatment decisions

Patient input was received from the CBCN and Rethink Breast Cancer. Patients providing input rated fatigue followed by pain as the most common symptoms of ABC that have the most severe impact on their QoL, with the greatest impact on the ability to work followed by the ability to sleep. The majority of patients experienced metastases to the bones, liver, and lungs and a small fraction had metastases to the brain. Patients reporting input to CBCN reported they had received surgery, chemotherapy, radiation therapy, and hormone therapy as treatment for their cancer. Rethink Breast Cancer reported that the most common current treatments received by patients included letrozole followed by tamoxifen, goserelin, and anastrozole. Fatigue, low blood cell counts, and insomnia were the most commonly reported side effects of current treatments, with fatigue being cited as the most difficult to tolerate. A large proportion of patients also cited financial impacts related to their cancer diagnosis and treatment, with the majority indicating the cost of prescription medications had a significant or some impact on their treatment decision-making and on QoL. Patients expressed concerns about pain management and management of chemotherapy side effects. They wanted to initiate treatment as early as possible following diagnosis and have access to hormone therapy and targeted therapies over chemotherapy (i.e. access to many treatment options). Patients expressed a strong desire to not undergo chemotherapy.

Patient values, experience on or expectations for treatment: Disease control, prolonging OS, maintenance of QoL, manageable side effects, and avoidance of chemotherapy

Overall, patient expectations for new treatments include delaying disease progression, prolonging life while maintaining QoL, having a manageable side effect profile, and avoiding chemotherapy. The majority of patients indicated they were willing to tolerate either some or a moderate impact on QoL from side effects in order to extend life expectancy. Additionally, patients highlighted the importance of having access to multiple treatment options so that they can make personal choices regarding their treatment based on their preferences.

Patients with first-hand experience with the ribociclib combination under review (but not necessarily as initial ET) reported that the combination was overall well tolerated and offered anecdotes that the treatment efficiently stabilized and controlled their disease. The side effects experienced by patients included mild nausea, fatigue, occasional indigestion, thinning of hair, and a reduced white blood cell count but were characterized by patients as very minimal and generally tolerable. Accordingly, all patients with ribociclib treatment experience who responded to Rethink Breast Cancer's survey unanimously recommended this treatment combination to other patients.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analyses of ribociclib plus NSAI and goserelin compared to NSAI plus goserelin were the focus of deliberation

The submitted economic model assessed the cost-effectiveness (clinical effects measured as life-years [LYs] gained) and cost utility (clinical effects measured by QALYs gained) of ribociclib plus NSAI and goserelin compared to NSAI plus goserelin as initial ET for women with pre- and peri-menopausal HR-positive, HER2-negative ABC who have not received prior ET for their advanced disease. To assess the comparative effectiveness of ribociclib plus NSAI and goserelin to other relevant comparators, the sponsor provided an updated model at the request of pCODR to include additional CDK 4/6 inhibitor-based therapies (palbociclib and abemaciclib with AI or fulvestrant).

Basis of the economic model: Clinical and economic inputs

The sponsor submitted a semi-Markov cohort model comprised of three health states (PFS, post-progression survival, and death) that included 66 tunnel states to allow the probabilities of death after progression to vary by time since progression, for the first five years after progression. The economic evaluation was based on clinical efficacy (PFS and OS), health utility, and safety data from MONALEESA-7 trial using on the most

recent data cut-off date (November 30, 2018) and relative efficacy estimates for comparators were sourced from the updated ITC conducted by the sponsor.

The costs considered in the economic evaluation included those for drugs and drug administration (non-oral drugs), follow-up and monitoring, post-progression treatments, treatment of AEs, and terminal care.

Drug costs: High drug cost

Ribociclib costs $0.42 per mg and $253.95 per day. At the recommended dose of 600 mg (three 200 mg tablets) taken orally once daily for days 1 to 21 of a 28-day cycle, ribociclib costs $5,332.95 per 28-day course.

Cost of ribociclib plus letrozole and goserelin:

- $678.01 per day
- $5,794.21 per 28-day course.

Cost of ribociclib plus anastrozole and goserelin:

- $677.58 per day
- $5,768.95 per 28-day course.

Cost-effectiveness estimates: High uncertainty in the cost-effectiveness of ribociclib plus NSAI and goserelin, need for price reduction

According to the sponsor's base-case (probabilistic) analysis, ribociclib plus NSAI and goserelin would result in incremental costs of $209,701 and incremental benefits of 1.42 additional LYs and 1.17 additional QALYs over a 15-year life-time horizon, for an estimated ICUR of $178,872 per QALY. Sensitivity and scenario analyses carried out by the sponsor demonstrated that the results were mainly driven by the unit cost of ribociclib, the HR for PFS, and PFS health utility values. The probability that ribociclib plus NSAI and goserelin is cost-effective were 0% and 37.3% at willingness-to-pay thresholds of $50,000 per QALY and $100,000 per QALY, respectively.

As requested by the EGP, the sponsor provided a scenario analysis whereby all CDK 4/6 inhibitors, including palbociclib and abemaciclib, and their combination with NSAI or fulvestrant were considered. Results of the sequential analysis showed that tamoxifen was the least expensive treatment but led to the smallest QALYs. NSAI alone, abemaciclib plus AI, and abemaciclib plus fulvestrant were dominated by palbociclib plus fulvestrant. The ICUR of ribociclib plus NSAI and goserelin versus palbociclib plus fulvestrant was $191,227 per QALY. The sponsor stated that the cost-effectiveness results should be interpreted with caution because the comparative efficacy of all CDK 4/6 inhibitors was based on an ITC that included trials consisting of different targeted populations (pre- and peri-menopausal versus post-menopausal women) and previous lines of treatment for ABC.

The EGP identified a number of limitations with the submitted economic evaluation, which included the following:

- structural uncertainty of the model: the semi-Markov cohort model structure with three health states and 66 tunnel states may not accurately represent the treatment pathway as patients with ABC can experience multiple progressions and lines of therapy after first-line treatment
- high uncertainty related to the long-term extrapolation of treatment efficacy: trial data based on a 45-month follow-up period were used to predict PFS and OS over a 15-year time horizon; and the OS prediction is highly uncertain given that the median OS in the ribociclib treatment group has not been reached
- concern that the method used to derive patients' transition probabilities from the PFS health state to death may inflate the impacts of ribociclib on life expectancy and QALYs: the model indirectly forces transition probabilities from death to be dependent on PFS
- inappropriate assumptions on end-of-life terminal care costs: the model assumed that the terminal care cost for patients with ABC was equal to patients diagnosed with esophageal cancer; however, given differences in treatments and care pathways for each cancer, the much higher terminal care cost associated with ABC should be used
- the EGP agreed with the sponsor's concern related to the ITC that informed the cost-effectiveness estimates of ribociclib plus NSAI and goserelin to relevant comparators: the comparative cost-effectiveness results from these analyses should be interpreted with caution given the significant clinical heterogeneity among the trials and the potential for unreliable cost-effectiveness estimates.

Except for the concerns related to structural uncertainty and the ITC, the EGP was able to make changes to the economic model in reanalyses to address limitations, which included the following:

- the uncertainty in the long-term efficacy of ribociclib plus NSAI and goserelin was assessed by shortening the time horizon; varying the parametric survival model used to predict long-term PFS and post-progression survival (PPS) data; and additionally, no incremental benefit of ribociclib plus NSAI and goserelin compared to NSAI and goserelin on PFS and PPS was assumed after the end of the trial
- the EGP assumed the same transition probability from PFS to death for all comparators
- the terminal care cost for patients with breast cancer was used as a one-time cost in reanalysis
- scenario analyses were performed to identify the upper and lower bound of EGP reanalyses, and price reduction scenario analyses were performed based on the sponsor's and EGP's best-case estimate.

In the EGP's best-case estimate, the incremental cost of ribociclib plus NSAI and goserelin was $180,936 and the incremental benefit gain was 1.08 LYs and 0.91 QALYs over a 10-year life-time horizon when compared to NSAI plus goserelin, for an estimated ICUR of $197,832 per QALY. The upper and lower bound of the ICUR estimate were $177,829 per QALY and $386,675 per QALY, respectively. The main factors influencing the extra cost and clinical effect are the time horizon and the extrapolation of PFS data after the end of the trial follow-up. The price reduction scenario analyses showed that a price reduction of 55% or greater would be needed to bring the ICUR lower than $100,000 per QALY and an 85% price reduction would be required to bring the ICUR lower than $50,000 per QALY.

The EGP concluded that the cost-effectiveness results are highly uncertain and dependent on the predicted clinical benefit of ribociclib plus NSAI and goserelin compared to NSAI plus goserelin beyond the trial follow-up. The cost-effectiveness of ribociclib plus NSAI and goserelin compared to other CDK 4/6 inhibitors and treatments other than NSAIs should be interpreted cautiously as the results are subject to important limitations related to the clinical heterogeneity of the trials included in the ITC that informs the clinical effectiveness estimates.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Additional resources required; budget impact may be underestimated

PAG identified the following factors that could impact the implementation of ribociclib plus NSAI and goserelin: there is potential risk for dosing error as the dosing of ribociclib is different from NSAI; pill burden is a concern as the recommended dose requires three tablets; additional health care resources will be required to monitor and treat toxicities (i.e., neutropenia and risk for QT prolongation), which include more frequent clinic visits, blood work, ECGs, and nursing and pharmacy time. PAG commented that in some jurisdictions, oral medications are not funded in the same manner as IV medications, which may limit accessibility of treatment for patients and necessitate application to Pharmacare programs that can pose a financial burden to patients in the way of co-payments and deductibles. PAG also requested clarity on factors related to currently funded treatments, the eligible patient population, and sequencing of treatments. Refer to Appendix 1 for pERC's recommendations pertaining to these issues.

The sponsor provided a BIA, based on an incidence approach, from the perspective of national and provincial health care payers to show the three-year potential budgetary impact of ribociclib plus NSAI and goserelin in pre- and peri-menopausal women with HR-positive, HER2-negative ABC who received no prior ET for advanced disease. The BIA included patients receiving first-line treatment for ABC as well as those with prior chemotherapy for ABC, and considered drug costs and treatment administration costs, but excluded mark-up and dispensing fees. Based on the sponsor's BIA, the factors that most influenced the BIA included medication costs, the percentage of breast cancer patients who are HR-positive, the total number of patients who are eligible for ribociclib plus NSAI and goserelin, and the market share of ribociclib. The EGP performed exploratory analyses to assess the impact of a variety of parameters on the budget impact. Varying the RDI of ribociclib by 25% did not have a large impact on the cumulative budgetary impact; however, if a 100% RDI is assumed, the three-year total budgetary impact would increase by 35.1%; additionally, if drug wastage is assumed for all medications, the three-year total budgetary impact would increase by 29.9%.

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
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

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

- Dr. Avram Denburg, who was not present for the meeting
- Dr. Anil Abraham Joy, who was excluded from deliberations and voting due to a conflict of interest
- Dr. Maureen Trudeau, who did not vote due to her role as the pERC Chair.

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

- Dr. Anil Abraham Joy who was excluded from deliberations and voting due to a conflict of interest
- Dr. Maureen Trudeau, who did not vote due to her role as the pERC Chair

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 ribociclib for pre- and peri-menopausal ABC, through their declarations, two members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, and one of these members was excluded from voting. For the Final Recommendation, two members had a real, potential, or perceived conflict, and based on application of the pCODR Conflict of Interest Guidelines, one member was 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.

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

PAG Implementation Questions	pERC Recommendation
• Information on whether results for ribociclib plus an AI can be generalized to: ○ Patients with inflammatory breast cancer ○ Men with ABC ○ Patients with HR-positive, HER2-positive ABC who are not eligible for further anti-HER2 treatments	○ Patients with inflammatory breast cancer were excluded from the MONALEESA-7 trial. pERC agreed with the CGP that it is clinically appropriate to follow the MONALEESA-7 trial design and not generalize the evidence to patients with primary inflammatory breast cancer. ○ Potential clinical benefit for male patients with ABC is usually extrapolated from trial data for female patients. pERC agreed that extrapolation of the data from the MONALEESA-2 trial (ribociclib plus letrozole) to male patients with ABC is reasonable for this indication. ○ pERC agreed with registered clinician input that there is limited evidence to extend the use of ribociclib with an AI to patients with HER2-positive breast cancer who are not eligible for further anti-HER2 treatments; therefore, the combination should not be used in these patients.
• Guidance on the appropriateness of: ○ Adding ribociclib for patients who are already on ET (e.g., anastrozole or letrozole) but not yet progressed ○ Use with other AIs ○ Switching patients who are already on another ET but not yet progressed to ribociclib ○ Switching ribociclib with abemaciclib or palbociclib for the respective indications if a patient is intolerant to one ○ Continuing treatment if there is oligoprogression	○ pERC agreed that at the time of implementing a funding recommendation it would be reasonable to add ribociclib to ET in order to address the short-term, time-limited need for patients who are currently on an AI (and ovarian suppression) and whose disease has not progressed. ○ To be consistent with other funded CDK 4/6 inhibitors, pERC agreed that it would be acceptable to use ribociclib with any AI, instead of limiting reimbursement to letrozole and anastrozole. ○ Patients with prior exposure to ET for ABC were excluded from the MONALEESA-7 trial; however, enrolled patients could have received exposure of ET for ABC within the following parameters prior to randomization: 14 days or less of tamoxifen or a NSAI with or without goserelin, or only goserelin for 28 days or less. pERC agreed that switching patients who have not progressed from another ET to ribociclib should follow the criteria in the trial, except for the time limited need at the time of a funding recommendation (as noted above). ○ pERC agreed with the CGP that switching from a different CDK 4/6 inhibitor (abemaciclib or palbociclib) to ribociclib (or vice versa) would be reasonable if a patient demonstrates intolerance; the choice of CDK 4/6 inhibitor will likely depend on the cause of intolerance. ○ pERC agreed with the CGP that if a patient has oligoprogression and is deriving clinical benefit overall in the judgment of the treating clinician, continuing treatment with ribociclib and an AI would be reasonable.
• Whether there is a preference for a specific CDK 4/6 inhibitor (ribociclib, abemaciclib, or palbociclib) or can they be considered therapeutically equivalent; under what circumstances is ribociclib preferred to abemaciclib and palbociclib?	• The sponsor provided an ITC to estimate the relative treatment effects of CDK 4/6 inhibitor combinations (palbociclib and abemaciclib combined with either AI or fulvestrant) but a critical appraisal of this analysis indicated the results should be interpreted with caution due to significant clinical heterogeneity in patient populations across the included trials that could impact their comparability to the MONALEESA-7 trial and lead to biased estimates of relative treatment effect. pERC agreed with the CGP that while most clinicians consider CDK 4/6 inhibitors therapeutically equivalent in terms of efficacy, there are notable differences in required monitoring and supportive care considerations that may make one CDK 4/6 inhibitor preferable to the others for individual patients. Palbociclib requires no routine ECG or liver function test monitoring like ribociclib, and abemaciclib can be

	complicated by dose-limiting diarrhea, which must be aggressively managed.
• Guidance on the appropriate sequencing of all available treatments for patients with HR-positive, HER2-negative ABC: ○ Whether there is a preference for ribociclib plus AI or fulvestrant in the endocrine-naive or sensitive ABC setting ○ What treatments patients can receive following ribociclib plus AI ○ If there is evidence to support retreatment with ribociclib or another CDK 4/6 inhibitor in patients whose disease has progressed on or after ribociclib ○ How everolimus-exemestane should be sequenced	○ pERC agreed with the CGP that access to fulvestrant has been problematic across Canada although the introduction of a generic formulation may expand availability. Ribociclib plus AI or fulvestrant have demonstrated clinical benefit in HR-positive, HER2-negative patient populations and clinical treatment decisions may depend partly on access to fulvestrant as well as on other factors such as patient preference or line of therapy. ○ pERC agreed with the CGP that treatment options after disease progression on ribociclib plus an AI can include rotation to a different single-agent AI (nonsteroidal to steroidal AI), tamoxifen, fulvestrant (if available), everolimus plus exemestane, or single-agent or combination cytotoxic chemotherapy, as well as clinical trial options depending on availability. ○ There is no evidence supporting retreatment with a CDK 4/6 inhibitor in the setting of disease progression on a CDK 4/6 inhibitor. ○ pERC agreed with the CGP's guidance on sequencing of everolimus plus exemestane: everolimus plus exemestane remains a treatment option for this patient population after disease progression on a CDK 4/6 inhibitor; however, it is unclear whether the clinical benefit of this combination is maintained in the context of prior CDK 4/6 exposure. Due to the robust nature of the clinical data supporting CDK 4/6 inhibitors as first-line therapy, as well as the fact that the majority of patients in the BOLERO-2 RCT supporting everolimus and exemestane were treated in the second-line setting, most clinicians would favour sequencing everolimus plus exemestane after a CDK 4/6 inhibitor combination.

AI = aromatase inhibitor; ABC = advanced or metastatic breast cancer; CDK = cyclin-dependent kinase; CGP = Clinical Guidance Panel; ECG = electrocardiogram; ET = endocrine-based therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; ITC = indirect treatment comparison; NSAI = nonsteroidal aromatase inhibitor; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; RCT = randomized controlled trial.