pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

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

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Ribociclib (Kisqali)	
Submitted Reimbursement Request: Ribociclib in combination with fulvestrant 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 (ABC), as initial therapy or following disease progression.	
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:** April 22, 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. Fulvestrant costs $1.98 per mg and $990.92 per day. At the recommended dose of 500 mg (two 5 mL injections) every 28 days on the first day of each cycle with an additional dose on day 15 of cycle 1, fulvestrant costs $1,981.84 per 28-day course for cycle 1 and $990.92 per 28-day course for subsequent cycles. Cost of ribociclib combined with fulvestrant: • $2,235.79 for cycle 1 • $1,244.87 for subsequent cycles • $8,305.71 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	pERC conditionally recommends the reimbursement of ribociclib (Kisqali) in combination with fulvestrant as initial therapy or following disease progression in patients with HR-positive, HER2-negative ABC if the following conditions are met: • cost-effectiveness improved to an acceptable level • feasibility of adoption addressed (budget impact). Eligible patients include men and post-menopausal women who have not received any prior treatment for ABC or have received up to one line of treatment for ABC. Pre-/peri-menopausal women rendered post-menopausal, either chemically or surgically, are eligible and should be treated with a luteinizing hormone-releasing hormone (LHRH) agonist or bilateral salpingo-oophorectomy. Treatment should be continued until disease progression or unacceptable toxicity. Patients should have good

reimbursement of the drug for the submitted reimbursement request.	performance status and not have active or uncontrolled metastases to the central nervous system. pERC made this recommendation because it was satisfied that compared to fulvestrant alone, there is a net clinical benefit of ribociclib plus fulvestrant 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 fulvestrant aligns with patients' values of delaying disease progression, 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 fulvestrant is not considered cost-effective compared to fulvestrant alone. pERC noted the cost-effectiveness results are highly uncertain due to the short-term follow-up of the MONALEESA-3 trial and are therefore largely dependent on the extrapolation of clinical benefit beyond the trial follow-up period. The comparative cost-effectiveness of ribociclib plus fulvestrant to other relevant cyclin-dependent kinase (CDK) 4/6-based comparators (i.e., palbociclib and abemaciclib with fulvestrant or aromatase inhibitors [AI]) 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 fulvestrant, which is driven by the high drug cost, the number of potentially eligible patients, and the market share of ribociclib plus fulvestrant; as well as 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 was concerned that the submitted budget impact may be underestimated and uncertain due to the lack of public funding for fulvestrant which is likely to limit the market share of ribociclib plus fulvestrant.

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 fulvestrant, 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.

Time-Limited Need for Patients Who Recently Initiated Treatment with Fulvestrant
At the time of implementing a funding recommendation for ribociclib plus fulvestrant, jurisdictions may want to consider addressing the short-term, time-limited need of adding ribociclib to patients who recently initiated treatment with fulvestrant. pERC noted that this approach would be appropriate given that patients have been able to receive compassionate supply fulvestrant.

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

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

SUMMARY OF pERC DELIBERATIONS

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, endocrine-based therapy (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). For those patients who do not receive a CDK inhibitor-based treatment in the first-line setting, the main competing alternative second-line hormonal treatments are exemestane with or without everolimus, tamoxifen, or single-agent fulvestrant. Fulvestrant is not funded in all provinces and therefore would only be accessible through private insurance or out-of-pocket payment in most jurisdictions. pERC acknowledged that everolimus plus exemestane has a clinical benefit but is also associated with considerable toxicity. Overall, pERC considered there is a need for new and effective therapies for patients with ABC that provide improvements in patient survival, have more favourable toxicity profiles, and improve QoL.

pERC deliberated the results of one randomized, multi-centre, double-blind, placebo-controlled, phase III trial (MONALEESA-3) that evaluated the efficacy and safety of ribociclib in combination with fulvestrant compared with placebo plus fulvestrant as either first-line (endocrine sensitive) or second-line (endocrine resistant) treatment for patients with post-menopausal, HR-positive, HER2-negative ABC. pERC noted that eligible patients in the first-line setting included patients whose disease had relapsed more than 12 months after completion of (neo)adjuvant ET with no subsequent treatment for ABC, or patients with de novo ABC. pERC also noted that eligible patients in the second-line setting included patients whose disease had relapsed on or within 12 months of completing (neo)adjuvant ET with no subsequent treatment for ABC (early relapse), or patients who had received up to one line of ET for ABC and had relapsed more than 12 months after completion of (neo)adjuvant ET and had progressed on or after subsequent ET for ABC, or who had ABC at the time of diagnosis that had progressed on or after ET with no prior (neo)adjuvant ET for early disease. 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 fulvestrant. For both outcomes, the treatment effect was consistent across patient subgroups, including by the use and type of prior ET (treatment naive, up to one line of ET, prior use of AI or tamoxifen); however, small sample sizes limited the interpretation of the data in a few patient subgroups. In addition, other secondary outcomes assessed in the trial, including objective response rate and time to chemotherapy, also favoured treatment with ribociclib plus fulvestrant, when compared to placebo plus fulvestrant. pERC discussed that male patients with ABC were also eligible for the MONALEESA-3 trial, although none were enrolled. Considering the potential clinical benefit for male patients with ABC is usually extrapolated from trial data for female patients, pERC agreed that extrapolation of the MONALEESA-3 trial data to male patients with ABC is also reasonable for this indication.

pERC deliberated the toxicity profile of ribociclib plus fulvestrant and noted that combination treatment with fulvestrant was associated with greater toxicity compared to fulvestrant monotherapy. Grade 3 or 4 AEs occurred in 78% of patients treated with ribociclib compared to 30% of patients treated with placebo; the most common of these was neutropenia, which occurred in 70% and 2% of patients, respectively. pERC noted that other cytopenias were increased in patients treated with ribociclib compared to patients in the placebo group, including anemia and leukopenia, in addition to other AEs such as nausea and vomiting, constipation, and alopecia. Other notable harms included QT prolongation of more than 60 ms, which occurred in 7% of patients in the ribociclib group versus less than 1% of patients in the placebo

group; and hepatic events, where grade 3 elevations in alanine aminotransferase (ALT) were observed in 7% of patients treated with ribociclib compared to 2% in patients treated with placebo. Serious AEs were reported in 29% of patients treated with ribociclib compared to 17% of patients treated with placebo; however, pERC noted that there were no serious AEs that occurred in more than 2% of patients in either treatment group. Treatment dose reductions and treatment discontinuation were both higher in patients treated with ribociclib, with discontinuations primarily attributable to increases in ALT or aspartate aminotransferase (AST). pERC acknowledged the overall greater toxicity of ribociclib plus fulvestrant compared with fulvestrant monotherapy but agreed with registered clinicians that AEs can be managed with dose adjustments and more extensive safety assessments (ECGs, liver function tests), as noted by the Clinical Guidance Panel (CGP). pERC therefore concluded that ribociclib plus fulvestrant has a manageable but not insignificant toxicity profile.

pERC discussed the health-related QoL data from the MONALEESA-3 trial, which focused on the time-to-10% deterioration in the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), the EuroQoL 5-Dimensions 5-Levels (EQ-5D-5L) questionnaire, and the Brief Pain Inventory Short Form (BPI-SF). EORTC-QLQ-C30, BPI-SF, and EQ-5D-5L scores 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 all other scales assessed (QLQ-C30 emotional, social and physical functioning; all BPI-SF pain scales; and the EQ-5D-5L Visual Analogue Scale [VAS]) all numerically favoured treatment with ribociclib plus fulvestrant but showed no difference between the treatment groups with respect to time-to-10% deterioration from baseline scores. pERC acknowledged, however, that the QoL results from the MONALEESA-3 trial may not accurately represent the QoL of patients treated with ribociclib plus fulvestrant as selection and confounding biases 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 fulvestrant.

Based on evidence from the MONALEESA-3 trial, pERC concluded that compared to fulvestrant monotherapy, there is a net clinical benefit to ribociclib plus fulvestrant in men and post-menopausal women with 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, absence of an apparent detriment in QoL outcomes, and the need for more first- and second-line treatment options for women with post-menopausal ABC.

In addition to the MONALEESA-3 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 combined with AI and fulvestrant as relevant comparators. The sponsor conducted several ITCs, each with a different patient population derived from the MONALEESA-3 trial: the full trial population, patients who are ET sensitive and receiving first-line therapy (which excluded patients with a disease-free interval or fewer than 12 months after [neo]adjuvant therapy), patients who are ET resistant who were either first-line ET refractory or were receiving second-line therapy, or patients receiving second-line therapy only. The ITCs included 16 trials that evaluated CDK 4/6 inhibitor-based therapies, AI, fulvestrant, tamoxifen, and everolimus with or without exemestane. Treatment comparisons were dependent on what trials could be connected in each ITC evidence network. Not all trials focused on a post-menopausal population, but subgroup data for patients who were post-menopausal were used when available. pERC noted that for the patient populations considered, the results of the ITCs suggest no evidence of a difference in efficacy between CDK 4/6 inhibitor-based therapies. The committee also noted the results of a naive comparison of safety data, based on the incidence of grade 3 and 4 events, that suggested CDK 4/6 inhibitors, as a group, appear to carry a higher risk of various cytopenias, most notably neutropenia, when compared to other therapies. However, the heterogeneity in patient populations 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 clinical heterogeneity across the trials that could impact their comparability to the MONALEESA-3 trial and produce biased estimates of relative treatment effect. In the absence of direct evidence and a lack of robust indirect evidence comparing the CDK 4/6 inhibitor combinations, pERC agreed with the CGP that most clinicians consider them therapeutically equivalent in terms of efficacy but there are differences in required monitoring and supportive care considerations that may make one drug preferable to the others for individual patients. The choice between CDK 4/6 inhibitor-based therapies will likely depend on multiple factors that include relative overall cost, availability of funded treatments in jurisdictions, patient values and preferences, and clinical factors such as tolerability to AEs.

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 fulvestrant 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 most of the patients providing input indicated a willingness to tolerate side effects and their impact on QoL in order to extend life expectancy. In addition, a high proportion of surveyed patients indicated that financial burdens imposed by their cancer treatments, including the cost of prescription medications, have a significant or some impact on their QoL and treatment decision-making. pERC noted that none of the patients providing input for this submission had direct experience with ribociclib and fulvestrant.

pERC deliberated the cost-effectiveness of ribociclib plus fulvestrant compared to fulvestrant alone for the treatment of post-menopausal women with HR-positive, HER-2 negative ABC who have received no prior ET or only one prior line of ET for their advanced disease. pERC noted that while the submitted model had the capacity to estimate the cost-effectiveness of ribociclib plus fulvestrant for the full population of the MONALEESA-3 trial as well as the ET-sensitive and ET-resistant patient subgroups, the Economic Guidance Panel (EGP) considered the evidence from subgroup analyses exploratory in nature as the trial was not designed to have statistical power to detect treatment effects within subgroups. The EGP had concerns that the lack of statistical power would increase the uncertainty of incremental cost-effectiveness estimates for the subgroups, and therefore, the EGP focused reanalyses to the full population of the MONALEESA-3 trial. pERC noted that the CGP endorsed the approach taken by the EGP as it indicated the biologic rationale underlying ET sensitivity and ET resistance is unclear. pERC discussed the key limitations of the submitted economic model identified by the EGP, which included the following: the high uncertainty related to the long-term extrapolation of clinical benefit for ribociclib plus fulvestrant over a 15-year time horizon based on short trial follow-up (27 months) and poor fitting parametric models to predict long-term outcomes; 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 and health utility and costs related to cytopenia. These limitations made it challenging to reliably estimate the incremental treatment effect of ribociclib plus fulvestrant. 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 outcome 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 upper and lower bounds of the estimate. pERC therefore concluded that compared to fulvestrant alone, ribociclib plus fulvestrant is 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 the MONALEESA-3 trial would help to decrease the uncertainty in the incremental treatment effect and inform on a more accurate estimate of cost-effectiveness of ribociclib plus fulvestrant. The submitted model also included cost-effectiveness estimates for ribociclib plus fulvestrant compared to other relevant CDK 4/6-based therapies. However, pERC agreed with the EGP 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 fulvestrant to other relevant CDK 4/6-based comparators could not be reliably estimated.

pERC considered the feasibility of implementing a reimbursement recommendation for ribociclib plus fulvestrant for the treatment of post-menopausal women with HR-positive, HER2-negative ABC. 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 with fulvestrant. pERC noted that for some patients ribociclib will 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, if the relative dose intensity of ribociclib is 100% in clinical practice, and considering the approach used to estimate treatment duration. pERC concluded that a reduction in the price of ribociclib would be required to decrease the predicted budget impact. However, pERC also noted the EGP's concerns that the submitted budgetary impact has considerable uncertainty given that fulvestrant is not covered by most public drug plans in Canada, and therefore lack of public coverage is likely to limit the market share and the budgetary impact of ribociclib with fulvestrant.

pERC also deliberated the input received from the 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.

EVIDENCE IN BRIEF

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

- 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)
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was provided by:

- two patient advocacy groups, CBCN and Rethink Breast Cancer
- one clinician group, CCO
- the PAG
- the sponsor, Novartis Pharmaceuticals Canada Inc.

The pERC Initial Recommendation was to conditionally recommend reimbursement of ribociclib in combination with fulvestrant as initial therapy or following disease progression in patients with 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 the sponsor, the two patient advocacy groups, and the PAG agreed with the Initial Recommendation, and the registered clinicians agreed in part with the Initial Recommendation. All Stakeholders supported early conversion of the Initial Recommendation to a Final Recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation. Clarifications related to the feedback provided by stakeholders that reflected the initial deliberation by pERC were added to the Final Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of ribociclib (Kisqali) in combination with fulvestrant for the treatment of post-menopausal women with HR-positive, HER2-negative ABC, as initial therapy or following disease progression.

Studies included: One multi-centre, double-blind, phase III randomized controlled trial (MONALEESA-3) was the focus of deliberation

The pCODR systematic review included one multi-centre, double-blind, phase III randomized controlled trial (RCT). MONALEESA-3 was a placebo-controlled, superiority trial conducted in 174 sites in 30 countries including Canada. The objective of the trial was to assess the efficacy of ribociclib in combination with fulvestrant for the treatment of men and post-menopausal women with HR-positive, HER2-negative ABC who had received no or only one line of ET for ABC. Randomization was stratified by the presence of lung or liver metastases and previous ET resulting in the following investigated groups of patients:

- Group A: Patients on first-line treatment (endocrine sensitive) whose disease relapsed fewer than 12 months after completion of (neo)adjuvant ET with no subsequent treatment for ABC, or patients with de novo ABC (no prior exposure to ET)
- Group B: Patients on second-line treatment or with early relapse (endocrine resistant) who received up to one line of treatment for ABC, and

i) whose disease relapsed on or within 12 months from completion of (neo)adjuvant ET, with no subsequent treatment for ABC, or
ii) relapsed more than 12 months after completion of (neo)adjuvant ET, and progressed on or after subsequent ET for ABC, or
iii) had ABC at time of diagnosis that progressed on or after ET for ABC with no prior (neo)adjuvant therapy for early disease.

Eligible patients were randomized in a 2:1 manner to either ribociclib or placebo, both on a background of fulvestrant. Patients in the intervention group received ribociclib 600 mg orally once daily for days 1 to 21 of a 28-day cycle and fulvestrant 500 mg intramuscularly on day 1 of each cycle with an additional injection on day 15 of cycle 1. Patients in the control group received placebo matched to ribociclib. Treatment continued until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. Dose modifications to ribociclib were allowed to manage AEs, including up to two dose reductions (first to 400 mg then to 200 mg), or dose interruption. Dose modifications to fulvestrant were not allowed.

At the time of the primary efficacy analysis the median duration of treatment exposure was longer in the ribociclib group at 15.8 months compared to 12 months in the placebo group. The median relative dose intensity for the ribociclib plus fulvestrant versus placebo plus fulvestrant treatment groups was 92.1% 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-3 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 fulvestrant compared to selected treatments for post-menopausal women with HR-positive, HER2-negative ABC who either had no or up to one line of prior ET for ABC. The ITC provided input for the pharmacoeconomic model in order to evaluate the cost-effectiveness and budget impact of ribociclib plus fulvestrant for the indication under review.

Patient populations: Stage IV, post-menopausal women, median age of 63 years, and Eastern Cooperative Oncology Group performance status of 0

The MONALEESA-3 trial enrolled 726 patients; 484 patients into the ribociclib plus fulvestrant group and 242 patients into the placebo group. Overall, the baseline characteristics of patients were well balanced between the trial treatment groups. Enrolled patients had a median age of 63 years, all were female, and 85% were white. About two-thirds (65%) of patients had an Eastern Cooperative Oncology Group performance status of 0, while the remainder had a status of 1. At trial entry, almost all patients (99%) had stage IV disease. Approximately 60% of patients had visceral metastases and approximately 21% had bone metastases only. The majority of patients (78%) had had more than 12 months elapse since their initial diagnosis of primary breast cancer. Approximately 19% of patients had de novo disease. The majority of patients had prior ET; in the ribociclib group approximately 49% of patients received up to one prior line of ET compared to 45% in the placebo group. Approximately 49% of patients were treatment naïve for ABC in the ribociclib group compared to 53% in the placebo group. Patients excluded from the trial included those who had documented evidence of relapse after 12 months or fewer from completion of (neo)adjuvant ET and subsequently progressed after one line of ET (with either an anti-estrogen or an AI) for ABC. Other excluded patients included those with symptomatic visceral disease, active uncontrolled central nervous system metastases, clinically significant uncontrolled heart disease or cardiac repolarization abnormality, inflammatory breast cancer, and prior receipt of chemotherapy, fulvestrant, or any CDK4/6 inhibitor.

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

The key efficacy outcomes deliberated by pERC included PFS (investigator-assessed) and OS. Other secondary efficacy outcomes assessed in the MONALEESA-3 trial included objective tumour response rate and time to chemotherapy; the results for these outcomes were consistent with the PFS and OS results.

At the data-cutoff date for the primary efficacy analysis (November 3, 2017), the median follow-up of patients was 20.4 months. At this time, there were 361 progression events across the trial, and fewer progression events with ribociclib plus fulvestrant (n = 210; 43% of patients) compared to placebo plus fulvestrant (n = 151; 62% of patients) for a statistically significant difference between treatment groups (hazard ratio [HR] = 0.59 [95% confidence interval [CI], 0.48 to 0.73]; P < 0.0001). The median PFS in the ribociclib group was 20.5 months (95% CI, 18.5 to 23.5) and was 12.8 months in the placebo group (95% CI,

10.9 to 16.3). The treatment effect remained consistent across various patient subgroups, including prior ET (treatment naive: HR = 0.58 [95% CI, 0.42 to 0.80]; and up to one line of ET: HR = 0.57 [95% CI, 0.42 to 0.74]), prior use of tamoxifen (HR = 0.62 [95% CI, 0.44 to 0.87]) and prior use of AI (HR = 0.67 [95% CI, 0.51 to 0.89]). The updated analysis of PFS based on a data cut-off date of June 3, 2019, after a median follow-up of 39.4 months, was consistent with the primary efficacy analysis; the median PFS was 20.6 months in the ribociclib group and 12.8 months in the placebo group (HR = 0.59 [95% CI, 0.49 to 0.71]).

OS was a key secondary outcome that was assessed at three planned interim analyses; one at the time of the PFS assessment (161 anticipated deaths), the second after 263 deaths, and the third after 351 deaths. There was no statistically significant difference in OS as of the primary analysis data cut-off date with 15% (n = 70) of patients in the ribociclib group and 21% (n = 50) of patients in the placebo group with an event of death at this time point. However, by the pre-planned second interim analysis (June 3, 2019), there was a total of 275 deaths; 35% (n = 167) of patients had an event of death in the ribociclib group compared to 45% (n = 108) of patients in the placebo group. This difference was statistically significant (HR = 0.72 [95% CI, 0.57 to 0.92]; P = 0.00455) as the P value crossed the pre-specified O'Brien-Fleming stopping boundary of P < 0.01129. The median OS was not reached in the ribociclib group and was 40.0 months (95% CI, 37.0 to not estimable) in the placebo group. Pre-specified subgroup analyses of OS suggested that the treatment effect remained consistent across various subgroups, including analyses based on line of therapy (first-line: HR = 0.70 [95% CI, 0.48 to 1.02] and early relapse or second-line: HR = 0.73 [95% CI, 0.53 to 1.00]).

Patient-reported outcomes: No deterioration in QoL

Patient-reported outcomes were evaluated in the MONALEESA-3 trial using the EORTC-QLQ-C30, the BPI-SF, and the EQ-5D-5L VAS. Health-related QoL was an exploratory outcome of the trial and the primary patient-reported outcome 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. Baseline assessments for the EORTC-QLQ-C30 were obtained from 93% of patients in MONALEESA-3; however, by the time end-of-treatment assessments were performed, data were only available from 41% of patients. The HR for deterioration in global health status and QoL was 0.80 (95% CI, 0.60 to 1.05), which numerically favoured ribociclib plus fulvestrant, but the CI indicated no difference between the treatment groups. Similar results were observed for time to deterioration in the other QLQ-C30 subscales, the pain subscales of the BPI-SF, and the EQ-5D-5L VAS.

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

As the MONALEESA-3 trial did not include a comparison to an active relevant comparator, the sponsor conducted an ITC to estimate the relative efficacy (PFS) and safety of ribociclib plus fulvestrant versus other treatments for patients with HR-positive, HER2-negative ABC. The ITC was conducted in order to provide inputs into 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 trials 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. The sponsor conducted several ITCs, each with a different patient population derived from the MONALEESA-3 trial: the full trial population, patients who were ET sensitive receiving first-line therapy (which excluded patients with a disease-free interval of fewer than 12 months after (neo)adjuvant therapy), patients who were ET resistant who were either first-line ET refractory or were receiving second-line therapy, or patients receiving second-line therapy only. A total of 16 trials were included in the ITC, which evaluated treatments including CDK 4/6 inhibitor-based therapies (palbociclib or abemaciclib), AI, fulvestrant, tamoxifen, and everolimus with or without exemestane. Treatment comparisons were dependent on what trials could be connected in each ITC evidence network. Not all trials focused on a post-menopausal population; however, when available, the authors tried to obtain subgroup data for patients who were post-menopausal. For the full population, the ITC results showed that all three CDK 4/6 inhibitors when combined with fulvestrant achieved a statistically significant improvement in PFS versus fulvestrant alone. Ribociclib plus fulvestrant was also shown to be superior to exemestane monotherapy, and there was no clear difference in efficacy between ribociclib plus fulvestrant and palbociclib plus fulvestrant or abemaciclib plus fulvestrant. There were no trials of palbociclib or abemaciclib plus fulvestrant in the first line (ET sensitive), thus comparisons for this patient subgroup were between ribociclib plus fulvestrant and CDK 4/6 inhibitors combined with an AI; results

from these comparisons showed no evidence of a difference in efficacy between ribociclib plus fulvestrant and the other CDK 4/6 inhibitors plus an AI. The ITC results for the second-line (ET resistant) and ET-refractory subgroups were similar as these subgroups used the same evidence network; results showed no differences in efficacy between ribociclib plus fulvestrant and the other CDK 4/6 inhibitors plus fulvestrant or everolimus plus exemestane. No conclusions could be drawn about the relative harms of the CDK 4/6 inhibitors, as only a naive comparison was presented; however, various cytopenias, most notably neutropenia, appear to be an adverse effect associated with the CDK 4/6 inhibitors. 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-3 trial and produce biased estimates of relative treatment effect.

Safety: Increased toxicity compared to fulvestrant alone, notable harms include neutropenia and other cytopenias

AEs of all grades occurred in 99% and 96% of patients in the ribociclib and placebo group. Grade 3 or 4 AEs occurred in 78% of patients treated with ribociclib and 30% of patients treated with placebo. The most common AE was neutropenia, which occurred in 70% of patients treated with ribociclib and 2% of patients treated with placebo. Grade 4 neutropenia occurred in 7% of patients receiving ribociclib versus none with those receiving placebo. Other cytopenias also occurred with greater frequency in the ribociclib group, including anemia (17% versus 5%) and leukopenia (28% versus 2%). AEs that occurred with a 10% difference between groups included nausea (45% versus 28%) and vomiting (27% versus 13%), constipation (25% versus 12%), and alopecia (19% versus 5%). QT prolongation occurred in 7% of patients in the ribociclib group versus fewer than 1% of patients in the placebo group. There were no cases of torsades de pointes.

AEs were the most common reason for dose reduction, and 33% of patients in the ribociclib group had at least one dose reduction compared to 3% in the placebo group. Serious AEs were reported in 29% of patients treated with ribociclib compared to 17% of patients treated with placebo. Of these events, 11% in ribociclib group and 3% in the placebo group were attributed to the study medication. Withdrawal due to AEs occurred more frequently in the ribociclib group at 17% versus in 6% of patients in the placebo group. These were primarily due to increases in ALT or AST.

There were 13 deaths (2.7%) in the ribociclib group and eight deaths (3.3%) in the placebo group during treatment or within 30 days of discontinuing treatment. Most of the deaths (seven in each group) were due to disease progression; however, there was one death in the ribociclib group that was suspected to be related to the study treatment. This patient died from acute respiratory distress syndrome and had baseline lung metastases. Updated harms data based on longer follow-up showed that AEs were consistent with the primary analysis.

Need and burden of illness: Need for additional treatment options

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), 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). For patients who do not receive a CDK inhibitor-based treatment in the first-line setting, the main competing alternative second-line ET are exemestane with or without everolimus, tamoxifen, or single-agent fulvestrant. Fulvestrant is currently not funded in all provinces and therefore is only accessible through private insurance or out-of-pocket payment in most jurisdictions. Unfortunately, all

endocrine-sensitive breast cancers inevitably develop acquired resistance to ET, necessitating a change in systemic treatment and thus there is a need for additional treatment options.

Registered clinician input: Preference for ribociclib over other CDK 4/6 inhibitors

One joint submission was received that included input from two clinicians on behalf of CCO on the use of ribociclib in combination with fulvestrant for the treatment of post-menopausal women with HR-positive, HER2-negative ABC. The clinicians commented that in the second-line setting, there is presently no funding for CDK 4/6 inhibitors. Based on the MONALEESA-3 trial, clinicians stated ribociclib plus fulvestrant is superior to fulvestrant monotherapy and exhibited an acceptable safety and tolerability profile. They also indicated a preference for its use in the endocrine-naive setting over abemaciclib and palbociclib. The clinicians noted that abemaciclib has more toxicities and although palbociclib has the most acceptable toxicity profile, the evidence supports the use of ribociclib. The CCO clinicians felt that there is limited evidence to extend the use of ribociclib plus fulvestrant to patients who are HER2-positive; however, they noted that male patients with breast cancer should have access despite the very limited evidence for use of fulvestrant in men. The clinicians highlighted that males were not excluded from the MONALEESA-3 trial, but none were recruited. 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; and fulvestrant is contraindicated in those with hypersensitivities to the drug or its excipients and in women who are pregnant or lactating.

Experience of patients with HR-positive, HER2-negative ABC: Fatigue and pain symptoms impact QoL, financial impacts 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 providing 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 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.

Rethink Breast Cancer and CBCN did not identify any patients with first-hand experience with ribociclib plus fulvestrant but reported on patients' experiences with ribociclib as initial ET. Some patients reported that ribociclib improved their cancer symptoms (fatigue, loss of appetite, and dyspnea) and QoL while patients reported side effects (fatigue, back and joint pain, neutropenia, and diarrhea) but indicated they were manageable. Patients also shared anecdotes that the treatment stabilized and controlled their disease.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analyses of ribociclib plus fulvestrant compared to fulvestrant alone in the full trial population 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 fulvestrant compared to fulvestrant alone for the treatment of women who are post-menopausal with HR-positive, HER-2 negative ABC who have received no prior ET or up to one prior line of ET for their advanced disease. The model had the capacity to estimate the cost-effectiveness of ribociclib plus fulvestrant for the full population of the MONALEESA-3 trial as well as the first-line (ET-sensitive) and second-line (ET-resistant) patient subgroups.

To assess the cost-effectiveness of ribociclib plus fulvestrant 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 data from two different data cut-off dates for the MONALEESA-3 trial; clinical efficacy (PFS and OS) and treatment duration data were based on the June 3, 2019, data cut-off, while health utility and safety data were based on the November 30, 2017, data cut-off. The 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.

Fulvestrant costs $1.98 per mg and $990.92 per day. At the recommended dose of 500 mg (two 5 mL injections) every 28 days on the first day of each cycle with an additional dose on day 15 of cycle 1, fulvestrant costs $1,981.84 per 28-day course for cycle 1 and $990.92 per 28-day course for subsequent cycles.

The cost of ribociclib combined with fulvestrant is:

- $2,235.79 for cycle 1
- $1,244.87 for subsequent cycles
- $8,305.71 per 28-day course.

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

According to the sponsor's base-case (probabilistic) analysis, which considers the full population of the MONALEESA-3 trial, ribociclib plus fulvestrant would result in incremental costs of $151,324 and incremental benefits of 1.19 additional LYs and 0.96 additional QALYs over a 15-year life-time horizon, for an estimated ICUR of $157,293 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 fulvestrant is cost-effective was 0% at a willingness-to-pay (WTP) threshold of $100,000 per QALY.

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 AI or fulvestrant were considered. Results of the sequential analysis showed that exemestane and fulvestrant were dominated by letrozole, as it was more expensive and led to fewer QALYs; and ribociclib plus fulvestrant and abemaciclib plus fulvestrant were extendedly dominated (i.e., had higher ICURs than the next most effective treatment) by palbociclib plus fulvestrant. Based on the sequential analysis, everolimus plus exemestane is cost-

effective compared to letrozole if the WTP threshold is less than $28,137 per QALY; tamoxifen is cost-effective if the WTP threshold is between $28,137 per QALY and $157,665 per QALY; and palbociclib plus fulvestrant is cost-effective if the WTP threshold is between $157,665 per QALY and $251,367 per QALY. The sponsor stated that the cost-effectiveness results should be interpreted with caution given that the comparative efficacy of all CDK 4/6 inhibitors was based on an ITC that included trials with significant heterogeneity in patient populations.

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

- comparative efficacy of ribociclib plus fulvestrant versus fulvestrant alone in ET-sensitive and ET-resistant subgroups: although the submitted model had the capacity to estimate the cost-effectiveness of ribociclib plus fulvestrant versus comparators for the full population and the ET-sensitive and ET-resistant patient subgroups of the MONALEESA-3 trial, the EGP considered the cost-effectiveness analyses for these subgroups exploratory in nature as the trial was not designed to have statistical power to detect treatment effects within subgroups; lack of statistical power to detect treatment effects within subgroups would increase the uncertainty of incremental cost-effectiveness estimates for the ET-sensitive and ET-resistant subgroups
- high uncertainty related to the long-term extrapolation of treatment efficacy: trial data based on 27-month trial follow-up were used to predict PFS and time-to-treatment discontinuation (TTD) or death over a 15-year time horizon; and additionally, the EGP had concerns that the parametric survival models used to predict PFS and TTD were a poor fit to the observed data, which make the survival prediction highly uncertain
- 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 ABC patients 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
- assumptions on health utility decrement and costs associated with decreased leukocyte count were equal to those associated with febrile neutropenia: according to the CGP, this assumption is inappropriate and likely overestimates the impact of the reduction in leukocyte count
- the EGP agreed with the sponsor's concern related to the ITC that informed the cost-effectiveness estimates of ribociclib plus fulvestrant 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 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 fulvestrant was assessed by shortening the time horizon and varying the parametric survival model used to predict long-term PFS, post-progression survival, and TTD data
- the EGP assumed the same transition probability from PFS to death for all comparators
- the EGP assumed that the cost and health utility decrement due to decreased leukocyte count to be the same as increased ALT or AST
- 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 the EGP's best-case estimate.

In the EGP's best-case estimate (full trial population), the incremental cost of ribociclib plus fulvestrant was $137,857 and the incremental benefit gain was 0.98 LYs and 0.80 QALYs over a 10-year life-time horizon when compared to fulvestrant alone, for an estimated ICUR of $171,723 per QALY with a range between $157,226 per QALY and $370,710 per QALY. The main factors influencing the extra cost and clinical effect are 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 50% or greater would be needed to bring the ICUR lower than $100,000 per QALY.

The EGP concluded that the cost-effectiveness results are highly uncertain and dependent on whether the predicted clinical benefit of ribociclib plus fulvestrant would sustain beyond the trial follow-up. The cost-effectiveness of ribociclib plus fulvestrant compared to other CDK 4/6 inhibitors and treatments in the ITC should be interpreted cautiously as the results are subject to important limitations related to 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 fulvestrant: pill burden is a concern as the recommended dose requires three tablets; the lack of funding of fulvestrant in provinces is a barrier to implementation; 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 fulvestrant in women who are post-menopausal with HR-positive, HER2-negative ABC who received no prior ET or up to one prior line of ET for advanced disease. The BIA included patients who would become eligible to initiate treatment with ribociclib and fulvestrant either as first- or second-line therapy and considered costs related to drug acquisition and administration and dispensing fees. Based on the sponsor's BIA, the factors that most influenced the BIA included medication costs, the percentage of ABC patients who are HR-positive, and the market share of ribociclib plus fulvestrant. However, the EGP performed exploratory analyses to assess the impact of a variety of parameters on the budget impact, which suggested that assuming 100% relative dose intensity for ribociclib, drug wastage for all medications, and treatment duration were key drivers of the three-year total budgetary impact that would increase the total budgetary impact by 39.5%, 27.5%, and 19.6%, respectively. The EGP believes the submitted budgetary impact has considerable uncertainty given that fulvestrant is not covered by most public drug plans in Canada; therefore, lack of public coverage is likely to limit the market share and the budgetary impact of ribociclib with fulvestrant.

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 voting due to a conflict of interest
- Dr. Maureen Trudeau, who did not vote due to her role as the pERC Chair.

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

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 plus fulvestrant post-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, one of these members 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 fulvestrant 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 who have received prior treatment for ABC with chemotherapy, fulvestrant or any CDK 4/6 inhibitor	○ Patients with inflammatory breast cancer were excluded from the MONALEESA-3 trial. pERC agreed with the CGP that it is clinically appropriate to follow the MONALEESA-3 trial design and not generalize the evidence to patients with primary inflammatory breast cancer. ○ Men were eligible for enrolment in the MONALEESA-3 trial, but none were recruited. Considering the potential clinical benefit for male patients with ABC is usually extrapolated from trial data for female patients, pERC agreed that extrapolation of the MONALEESA-3 trial data 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 plus fulvestrant to patients who have HER2-positive breast cancer who are not eligible for further anti-HER2 treatments; therefore, the combination should not be used in these patients. • There is no evidence supporting the clinical benefit of ribociclib plus fulvestrant for patients with prior CDK 4/6 plus AI exposure in the ABC setting; and it is unknown if changing the ET backbone and continuing with CDK 4/6 therapy (i.e., changing an AI to fulvestrant) provides clinical benefit in the second-line or beyond-treatment setting. pERC disagreed with the CGP and would not recommend the use of ribociclib and fulvestrant for ABC patients with disease progression on fulvestrant alone. Although prior exposure to chemotherapy in the advanced setting was not permitted in the MONALEESA-3 trial, pERC agreed with the CGP that it would be reasonable to consider ribociclib plus fulvestrant as a treatment option following completion of first-line chemotherapy.
• Guidance on the appropriateness of: ○ Adding ribociclib for patients who are already on ET (e.g., fulvestrant) but not yet progressed ○ 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 fulvestrant whose disease has not progressed. ○ pERC agreed that a switch in ET could be considered; however, it would also be reasonable to continue with first-line therapy, reserving ribociclib plus fulvestrant for second-line treatment upon disease progression. ○ 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 plus fulvestrant 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 performed an ITC to estimate the relative treatment effects of CDK 4/6 inhibitor combinations in different groups of patients from the MONALEESA-3 trial (full trial population, patients who are ET sensitive [first-line], and patients who are ET resistant [second-line]) but a critical appraisal of this analysis indicated the results should be interpreted with caution due to the heterogeneity in patient populations across the included trials that could impact their comparability to the MONALEESA-3 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 drug 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 fulvestrant ○ 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 has demonstrated clinical benefit in ET-sensitive patients and in this group 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 fulvestrant can include single-agent AI (nonsteroidal or steroidal AI), tamoxifen, everolimus plus exemestane, or single-agent or combination cytotoxic chemotherapy, as well as clinical trial options depending on availability. • There is currently 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 as to 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 plus exemestane were treated in the second-line setting, most clinicians would favour sequencing everolimus and everolimus 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; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; RCT = randomized controlled trial.