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ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Final Economic Guidance Report

Ribociclib (Kisqali) for Advanced or Metastatic Breast Cancer

June 4, 2020

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis was submitted to pCODR by the sponsor, Novartis Pharmaceuticals Canada Inc., and compared the combination of ribociclib, non-steroidal aromatase inhibitors (NSAI) including anastrozole or letrozole, and luteinizing hormone-releasing hormone agonist (LHRH) goserelin (GOS) to NSAI + GOS or tamoxifen + GOS for the treatment of advanced breast cancer (ABC) in pre- and peri- menopausal women with hormone receptor (HR)-positive, HER2-negative ABC who have received no prior endocrine therapy (ET) for ABC over a time horizon of 15 years. This is consistent with the reimbursement request and Health Canada indication. The analysis was conducted from the perspective of the Canadian healthcare system.

Table 1. Submitted Economic Model

Reimbursement Request/Patient Population Modelled	Aligns with the reimbursement request
Type of Analysis	<i>Cost-utility analysis and cost-effectiveness analysis</i>
Type of Model	<i>Semi-Markov, cohort model</i>
Comparator	<i>NSAI + GOS or TAM + GOS</i>
Year of costs	<i>Not reported</i>
Time Horizon	<i>15 years</i>
Perspective	<i>Government</i>
Cost of ribociclib	<ul style="list-style-type: none"> • \$0.42 per mg (200 mg per tablet) • \$253.95 per day • \$5,332.95 per 28-day course
Cost of NSAI: letrozole <i>* Price Source: IQVIA health care database</i> <i>[Date: not reported]</i>	<ul style="list-style-type: none"> • \$0.55 per mg (2.5 mg per tablet) • \$1.38 per day • \$38.58 per 28-day course
Cost of NSAI: anastrozole <i>* Price Source: IQVIA health care database</i> <i>[Date: not reported]</i>	<ul style="list-style-type: none"> • \$0.95 per mg (1 mg per tablet) • \$0.95 per day • \$13.33 per 28-day course
Cost of GOS <i>* Price Source: IQVIA health care database</i> <i>[Date: not reported]</i>	<ul style="list-style-type: none"> • \$117.41 per mg (3.6 mg per vial) • \$422.68 per day • \$422.68 per 28-day course
Cost of tamoxifen <i>* Price Source: IQVIA health care database</i> <i>[Date: not reported]</i>	<ul style="list-style-type: none"> • \$0.02 per mg (20 mg per tablet) • \$0.35 per day • \$9.80 per 28-day course
Cost of ribociclib + NSAI (letrozole) + GOS	<ul style="list-style-type: none"> • \$678.01 per day • \$5,794.21 per 28-day course
Cost of ribociclib + NSAI (anastrozole) + GOS	<ul style="list-style-type: none"> • \$677.58 per day • \$5,768.95 per 28-day course
Cost of ribociclib + tamoxifen + GOS	<ul style="list-style-type: none"> • \$676.98 per day • \$5,765.43.38 per 28-day course
Model Structure	<i>A semi-Markov, cohort model with three health states (progression-free survival, post-progression survival, and death) was developed. The model includes 66 tunnel states to allow the probabilities of death after progression to vary</i>

	<i>by time since progression for the first five years after progression.</i>
Key Data Sources	<ul style="list-style-type: none"> • <i>MONALEESA-7 trial (1) (data cut: November 30, 2018): Efficacy data, AE rates, and health utility values</i> • <i>ITC report from the Sponsor (2): Efficacy data</i>

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. However, the CGP considers that palbociclib plus letrozole, abemaciclib plus aromatase inhibitor (AI), palbociclib plus fulvestrant, and abemaciclib plus fulvestrant are also clinically relevant comparators. As requested by pCODR, the Sponsor included these comparators in modifications to the main analysis. This additional analysis was however based on an indirect treatment comparison (ITC) (2). The pCODR Methods Team’s appraisal of the ITC raised concerns about differences in baseline and clinical characteristics of patients included in the trials informing the ITC. The Economic Guidance Panel (EGP) believes that the concern related to heterogeneity in patient populations would cause considerable uncertainty in the comparative cost-effectiveness of ribociclib + NSAI + GOS and other treatments. Additionally, the EGP and CGP agree that the comparative effectiveness of ribociclib + NSAI + GOS versus tamoxifen + GOS is highly uncertain and dependent on how well a statistical model fits data observed from the MONALEESA-7 trial. More importantly, the EGP notes that tamoxifen is not part of Health Canada’s approved indication and the reimbursement request due to concerns related to QT interval prolongation. This EGP report therefore focuses on the comparison of ribociclib + NSAI + GOS and NSAI + GOS. The other treatments were included as exploratory analyses.

Relevant issues identified included:

- The CGP concluded that there is a net overall clinical benefit of ribociclib in addition to NSAI plus ovarian suppression for pre-/peri-menopausal women with incurable HR-positive, HER2-negative ABC based on one high-quality randomized, double-blind, placebo-controlled trial (MONALEESA-7), which demonstrated a clinically meaningful prolongation in progression-free survival (PFS) and overall survival (OS), an acceptable safety profile and no apparent detriment on health-related quality of life (QOL). This is reflected in the submitted economic analysis.
- The CGP noted that an exploratory analysis of survival of patients who moved onto subsequent therapy after disease progression revealed similar exposure to post-progression therapies between the two treatment groups with 68.5% of patients in the ribociclib group and 73.2% in the placebo group receiving post-progression therapies. Thus, significant differences in post-progression treatments are unlikely to influence the observed OS benefit reported. The use of post-progression therapies was adequately considered in the submitted economic analysis.
- The MONALEESA-7 trial reported that the use of subsequent CDK 4/6 inhibitors was lower in the ribociclib group compared to the placebo group (10% versus 19%, respectively). The impact of subsequent use of CDK 4/6 inhibitors on total costs was accounted for in the submitted model. The EGP was unable to assess the impact of subsequent CDK 4/6 inhibitors on PFS or OS as data regarding the clinical benefit of CDK 4/6 inhibitors after progression are unavailable.
- The CGP acknowledged that no unexpected toxicities were observed in the MONALEESA-7 trial. Important adverse events were considered in the submitted economic model.

Summary of registered clinician input relevant to the economic analysis

Two registered clinicians who contributed input for this submission considered ribociclib + AI + LHRH a new first-line treatment option for pre- and peri- menopausal women with HR-positive, HER2-negative ABC. The clinicians stated the combination is superior to ET alone and has an acceptable toxicity profile. The clinicians preferred ribociclib + AI + LHRH in the first-line setting over palbociclib, abemaciclib, and ribociclib + fulvestrant based on the results of the clinical trial evidence for this patient population. The submitted economic analysis considered clinical outcomes, including OS, PFS and side effects of ribociclib, raised by the registered clinicians. Alternative treatments for pre- and peri- menopausal women with HR-positive, HER2-negative ABC were considered in the modifications to the main analysis performed by the Sponsor.

Summary of patient input relevant to the economic analysis

Patients considered treatment effectiveness, extending survival without compromising QOL, manageable side effects, and cost and accessibility of treatments as the important factors for their treatment decisions. Patients who had treatment experience with the combination of ribociclib + AI + LHRH were satisfied with the treatment efficacy noting it stabilized and controlled their disease as well as improved their QOL. Patients experienced minimal and tolerable side effects, such as mild nausea, fatigue, and low white blood cell count. The submitted economic analysis considered disease progression, life expectancy, QOL, and important side effects of ribociclib, including low white blood cell count and neutropenia.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for ribociclib which are relevant to the economic analysis:

- Additional healthcare resources that may be required to monitor toxicities and drug-drug interactions routinely. The high incidence of neutropenia and risk for QT interval prolongation and hepatobiliary toxicities may lead to more frequent visits to oncologists and bloodwork. This factor was considered in the submitted economic analysis.
- The oral route of administration is an enabling factor. However, ribociclib has a different dosing schedule from the NSAI letrozole and anastrozole; this may cause confusion for some patients and pose a risk of dosing error. The economic analysis adequately considered this factor by using the actual drug dosages observed in the MONALEESA-7 trial.
- PAG was concerned about the impact of post-progression therapies, particularly the use of everolimus and exemestane after ribociclib. This concern was not addressed in the submitted economic analysis. The EGP addressed this concern by increasing the proportion of everolimus and exemestane usage in the subsequent lines of therapies by 20%.
- PAG sought to know which CDK 4/6 inhibitor was the most cost-effectiveness and under what circumstance. The Sponsor provided the results of modifications to the main analysis that considered relevant CDK 4/6 inhibitors. However, the results of these analyses are highly uncertain due to heterogeneity in patient populations of the trials included in the ITC.
- As ribociclib is an add-on therapy to letrozole or anastrozole, the treatment is expected to add a large budget impact to the healthcare system. This concern was addressed in the submitted budget impact analysis.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Probabilistic Estimates

Estimates (range/point)	Submitted	EGP Reanalysis	
		EGP's best case	Lower bound, Upper bound
ΔE (LY)	1.42	1.08	0.48, 1.42
Progression-free	1.53	1.25	0.51, 1.80
Post-progression	-0.11	-0.17	-0.23, -0.11
ΔE (QALY)	1.17	0.91	0.43, 1.17
Progression-free	1.26	1.04	0.47, 1.47
Post-progression	-0.09	-0.12	-0.17, -0.09
ΔC (\$)	209,701	180,936	165,534, 208,479
ICER estimate (\$/QALY)	178,872	197,832	177,829, 386,675

The submitted PSA suggested that the probabilities that ribociclib + NSAI + GOS is cost-effective were 0% and 37.3% at the willingness to pay thresholds of \$50,000/QALY and \$100,000/QALY, respectively.

The main assumptions and limitations with the submitted economic evaluation were:

- **Model structure.** The Sponsor used a semi-Markov, cohort model with three health states including PFS, post-progression survival (PPS) and dead. Although 66 tunnel states were used to allow the variation in the probabilities of death by time since progression, the EGP was concerned that using three health states may not be able to accurately represent the treatment pathway as a patient can experience multiple progressions after first-line treatment. Additionally, the tunnel states did not account for the potential health utility decrement due to subsequent therapies. A sequence economic model that accounts for subsequent lines of therapies would have been more appropriate. However, this type of model requires more data from multiple studies to populate the parameters for each therapy line. The impact of this structural uncertainty on the incremental cost-utility ratios (ICURs) is unclear. The EGP was unable to assess the implications of this limitation.
- **Comparators.** The Sponsor considered NSAI (letrozole or anastrozole) and tamoxifen as comparators. The CGP believes that it is reasonable to include palbociclib in combination with letrozole as they are used in practice. A survey of medical oncologists conducted by the Sponsor suggested that greater than 10% of survey respondents reported using palbociclib plus letrozole as treatment for pre-/peri-menopausal patients who have received no prior ET for ABC. Abemaciclib in combination with NSAI, abemaciclib in combination with fulvestrant, and palbociclib in combination with fulvestrant should also be considered as they recently received positive reimbursement recommendations. As requested by the EGP, the Sponsor provided additional modifications to the main analysis that considered all CDK 4/6 inhibitors. However, these supplemental results should be interpreted with caution due to differences in the baseline and clinical characteristics of patients enrolled in each trial. The MONALEESA-7 trial is the only trial that focused on pre-/peri-menopausal patients with HR-positive, HER2-negative ABC. The EGP and the pCODR Method's Team agree with the Sponsor's caution.
- **Efficacy of ribociclib + NSAI + GOS versus tamoxifen + GOS.** The comparative efficacy of ribociclib + NSAI + GOS versus tamoxifen + GOS was derived by performing a Cox regression based on a subgroup of the MONALEESA-7 trial participants who did not receive a combination of ribociclib and tamoxifen. The estimated comparative efficacy is

therefore based on how well the Cox regression fits with the MONALEESA-7 trial data. Given that the submitted economic analysis was based on the subgroup of MONALEESA-7 trial participants who received NSAI as the endocrine partner and that tamoxifen was not part of Health Canada's approved indication and the reimbursement request, the EGP considers the economic analysis of ribociclib + NSAI + GOS versus tamoxifen + GOS an exploratory analysis.

- Long-term efficacy of ribociclib in combination with NSAI and GOS. The Sponsor extrapolated long-term transition probabilities for PFS, PPS, and death as well as time to treatment discontinuation (TTD) from the MONALEESA-7 trial using parametric survival models. The prediction is highly uncertain given that at the data cut-off date the trial follow-up was 45 months and the median OS had not been reached. Shortening of the time horizon will increase the ICUR, causing ribociclib in combination with NSAI and GOS to be less favourable.
- Effect of ribociclib in combination with NSAI and GOS on transition from PFS to death. The Sponsor indirectly derived the probabilities that patients transition from a PFS state to a dead state by combining estimates of the probability of PFS events with estimates of the probability that a PFS event is death. Although this approach is reasonable given a small proportion of death among patients without progression observed in the MONALEESA-7 trial, the estimated probability of death may inflate the impacts of ribociclib + NSAI + GOS on life expectancy and quality-adjusted life years (QALYs) because the submitted model indirectly forces transition probabilities from to death to be dependent on PFS.
- End-of-life costs. The Sponsor assumed that the terminal care cost for ABC patients was equal to those diagnosed with esophageal adenocarcinoma (3). The EGP disagrees with this assumption given the difference in treatments and care pathways for each cancer. Using the terminal care cost specific to breast cancer (4) is likely to decrease the ICUR because this terminal care cost is much higher than the cost used by the Sponsor (\$22,263 versus \$9,004).
- Changes in health utility values associated with health states and adverse events (AEs), as well as costs associated with AEs have minimal impacts on the ICURs of ribociclib + NSAI + GOS versus NSAI + GOS.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

- Omission of important comparators. As requested by the EGP, the Sponsor provided additional modifications to the main analysis whereby all CDK 4/6 inhibitors, including palbociclib and abemaciclib, and their combination with NSAI or fulvestrant were considered. Results of the analysis showed that tamoxifen was the least expensive treatment but led to the smallest QALYs. NSAI, abemaciclib + AI, abemaciclib + fulvestrant were dominated by palbociclib + fulvestrant. The ICUR of ribociclib + NSAI versus palbociclib + fulvestrant was \$191,227/QALY (Table 3). These cost-effectiveness results should be interpreted with caution because the comparative efficacy of all CDK 4/6 inhibitors was based on an ITC (2) that included trials consisting of different targeted populations (pre/peri menopausal versus post-menopausal women) and previous lines of treatment for ABC.

Table 3. Submitted Additional Modifications to the Main analysis Considering All CDK 4/6 Inhibitors (Sequential Probabilistic Analysis)

Treatment [#]	Cost	QALYs	ΔC	ΔQALY	ICUR
Tamoxifen	\$110,269	2.3041	-	-	-
Palbociclib + AI	\$111,507	3.2168	\$1,238	0.9127	\$1,357
NSAI	\$121,404	3.2470	\$9,897	0.0302	Dominated
Abemaciclib + AI	\$111,742	3.2796	-\$9,663	0.0226	Dominated
Abemaciclib + fulvestrant	\$113,173	3.2711	\$1,431	0.0015	Dominated
Palbociclib + fulvestrant	\$111,582	3.2714	\$1,591	0.0003	\$1,376*
Ribociclib + NSAI	\$331,105	4.4194	\$219,523	1.1480	\$191,227**

Note: [#]all treatments include goserelin, *compared to palbociclib + AI, **compared to palbociclib + fulvestrant.

- Long-term efficacy of ribociclib + NSAI + GOS. The Sponsor used trial data with a 45-month follow-up period to predict PFS and OS over 15 years. The OS prediction is highly uncertain given that the median OS from the MONALEESA-7 trial has not been reached. The EGP assessed the uncertainty in the PFS and PPS data by shortening a model time horizon from a patient lifetime (15 years) to 10 and 5 years. Further, the EGP assessed the uncertainty in the long-term efficacy of ribociclib + NSAI by varying the parametric survival model used to predict long-term PFS and PPS data. Additionally, the EGP assumed no incremental benefit of ribociclib + NSAI compared to NSAI or tamoxifen on PFS and PPS after the end of the trial. The ICURs are highly sensitive to shortening of the time horizon and to variation in parametric survival models used to predict long-term PFS data.
- Transition probabilities from PFS to death. The Sponsor indirectly derived the probabilities that patients transition from a PFS state to a dead state by combining estimates of the probability of PFS events with estimates of the probability that a PFS event is death. Given that the median OS data for patients receiving ribociclib + NSAI + GOS in the MONALEESA-7 trial has not been reached, the EGP assumed the same transition probability from PFS to death to all comparators. Assuming no extra survival benefit of ribociclib + NSAI + GOS compared to NSAI + GOS or tamoxifen + GOS increases the ICURs substantially.
- Costs of end-of-life care. The terminal care cost for patients with breast cancer (4) was used as a one-time cost in the EGP reanalysis. Increased end-of-life care cost reduces the ICURs of ribociclib + NSAI + GOS.
- The EGP also assessed the impacts of health utility values associated with health states, as well as health utility value and cost associated with low white blood cell count. These factors had minimal impact on the ICURs.
- The EGP conducted a price reduction scenario analysis based on the Sponsor's and the EGP's Best Estimate. A price reduction of 55% or greater for ribociclib was needed to make the ICUR of ribociclib + NSAI + GOS lower than \$100,000/QALY.

Table 4: Detailed Description of EGP Probabilistic Reanalysis

One-way and multi-way sensitivity analyses					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Sponsor's best case) vs. NSAI + GOS	\$209,701	1.17	1.42	\$178,872	-
[LOWER BOUND]					
1. Assuming the cost and health utility decrement due to decreased leukocyte is equal to increased AST/ALT	\$209,509	1.17	1.42	\$178,708	-\$164
2. Updating end-of-life cost	\$208,521	1.17	1.42	\$177,865	-\$1,007
3. Long-term prediction for PFS: restricted generalized Gamma	\$209,265	1.20	1.46	\$173,976	-\$4,896
4. Long-term prediction for PFS: trial data + restricted log-normal	\$209,719	1.19	1.43	\$176,736	-\$2,136
5. Long-term prediction for PFS: trial data + restricted generalized Gamma	\$209,357	1.21	1.47	\$173,040	-\$5,832
6. Long-term prediction for PPS: Gompertz	\$209,825	1.18	1.43	\$177,815	-\$1,057
7. Long-term prediction for PPS: RCS Weibull	\$209,652	1.18	1.42	\$178,406	-\$466
8. Long-term prediction for PPS: trial data + Gompertz	\$209,778	1.18	1.42	\$177,971	-\$901
9. Long-term prediction for PPS: trial data + RCS Weibull	\$209,570	1.17	1.42	\$178,679	-\$193
Lower estimate of above four parameters [1,2,5,6]	\$208,479	1.17	1.42	\$177,829	-\$1,043
[UPPER BOUND]					
10. Long-term prediction for PFS: unrestricted generalized Gamma	\$194,465	0.68	0.78	\$287,433	\$108,561
11. Long-term prediction for PFS: trial data + unrestricted generalized Gamma	\$194,263	0.65	0.75	\$296,601	\$117,729
12. Long-term prediction for TTD: trial data + parametric survival models (restricted log-normal for ribociclib, restricted Gompertz for NSAI, restricted Weibull	\$211,978	1.17	1.42	\$180,760	\$1,888

<i>for GOS)</i>					
13. Long-term prediction for PPS: trial data + Weibull	\$209,434	1.17	1.41	\$179,140	\$268
14. Shorten a time horizon to 5 years	\$130,228	0.45	0.50	\$287,769	\$108,897
15. Shorten a time horizon to 10 years	\$182,365	0.91	1.08	\$199,396	\$20,524
16. Assuming no additional PFS benefit from ribociclib + NSAI + GOS after the end of the trial follow-up	\$169,032	0.51	0.58	\$331,788	\$152,916
17. Assuming the same transition probability to death from PFS state for ribociclib + NSAI and NSAI	\$203,464	0.93	1.09	\$219,857	\$40,985
Upper estimate of above six parameters [11,12,13,15,16,17]	\$165,534	0.43	0.48	\$386,675	\$207,803
EGP's Reanalysis for the Best Case Estimate					
EGP's best case estimate of above two parameters [2,15]	\$180,936	0.91	1.08	\$197,832	-\$18,960

Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICUR, incremental cost-utility ratio; NSAI, non-steroidal aromatase inhibitor; GOS, goserelin; PFS, progression-free survival; PPS, post-progression survival; TTD, time to discontinuation.

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis (BIA) include medication costs, the total number of patients who are eligible for ribociclib + NSAI + GOS, and the market share of ribociclib in the first-line setting. The higher acquisition cost of ribociclib, the greater number of patients who are eligible for ribociclib + NSAI + GOS, and the increased market share of ribociclib in the first-line setting increased the total budgetary impact of ribociclib. Varying a relative dose intensity (RDI) by 25% did not have a large impact on the cumulative budgetary impact. However, if a 100% RDI is assumed for ribociclib, the 3-year budgetary impact would increase to \$41,668,669 and \$130,860,908 for Ontario and Canada, respectively. Additionally, if drug wastage is assumed for all medications, the 3-year total budgetary impact would rise by 29.9%.

Key limitations of the BIA model include the approach that the Sponsor used to approximate mean TTD from median TTD. This approach assumed that TTD data follows an exponential distribution. This assumption was not consistent with the TTD distributions used in the submitted economic model whereby log-normal (restricted), Gompertz (restricted), and Weibull (restricted) distributions were assumed for TTD data of ribociclib, NSAI, and GOS, respectively. However, replacing TTD data for ribociclib, NSAI, and GOS with mean TTD used in the economic model leads to a slight reduction in the budgetary impact.

1.6 Conclusions

The EGP's best estimates of ΔC and ΔE for ribociclib + NSAI + GOS are:

- Between \$177,829/QALY and \$386,675/QALY when compared to NSAI + GOS.
- The EGP's best estimate is \$197,832/QALY.
- The extra cost of ribociclib + NSAI + GOS compared to NSAI + GOS is between \$165,534 and \$208,479. The two key factors that influence extra costs are time horizon and the assumption of PFS data after the end of the trial follow-up.
- The extra clinical effect (ΔE) of ribociclib + NSAI + GOS compared to NSAI + GOS is between 0.43 and 1.17 QALYs. The two key factors that influence extra effects are time horizon and the assumption of PFS data after the end of the trial follow-up.

Overall conclusions of the submitted model:

The model structure and assumptions were well-justified. The cost-effectiveness results are highly uncertain and depend on the predicted clinical benefit of ribociclib + NSAI + GOS compared to NSAI + GOS beyond the trial follow-up. The cost-effectiveness of ribociclib + NSAI + GOS compared to other CDK 4/6 inhibitors and treatments other than NSAIs should be interpreted cautiously as the results are subject to important limitations concerning the clinical heterogeneity of patient populations included in the ITC.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Breast Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of ribociclib for pre-/peri-menopausal ABC. A full assessment of the clinical evidence of ribociclib for pre-/peri-menopausal ABC is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

REFERENCES

1. Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *The Lancet Oncology*. 2018;19(7):904-15. Epub 2018/05/29. doi: 10.1016/s1470-2045(18)30292-4.
2. Novartis Pharmaceuticals Corporation. Indirect Treatment Comparisons of Ribociclib plus Fulvestrant versus Selected Other Treatments for Men and Postmenopausal Women with HR+/HER2- Advanced Breast Cancer who Have Received No or Only One Prior Line of Endocrine Therapy. Brookline, MA: Policy Analysis Inc., 2019.
3. Thein HH, Jembere N, Thavorn K, Chan KKW, Coyte PC, de Oliveira C, et al. Estimates and predictors of health care costs of esophageal adenocarcinoma: a population-based cohort study. *BMC cancer*. 2018;18(1):694. Epub 2018/06/28. doi: 10.1186/s12885-018-4620-2.
4. de Oliveira C, Pataky R, Bremner KE, Rangrej J, Chan KK, Cheung WY, et al. Phase-specific and lifetime costs of cancer care in Ontario, Canada. *BMC Cancer*. 2016;16(1):809.
5. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *British Journal of Cancer*. 2006;95(6):683-90.
6. Guertin JR, Feeny D, Tarride JE. Age- and sex-specific Canadian utility norms, based on the 2013-2014 Canadian Community Health Survey. *Canadian Medical Association Journal*. 2018;190(6):E155-e61.
7. pan-Canadian Oncology Drug Review. pan-Canadian Oncology Drug Review: Final Economic Guidance Report Abemaciclib (Verzenio) for Metastatic Breast Cancer [Internet]. Toronto: pCODR.2019. July 5, 2019. Available from: https://www.cadth.ca/sites/default/files/pcodr/Reviews2019/10161AbemaciclibMBC_fnEGR_NOR_EDACT-ABBREV_Post_05Jul2019_final.pdf
8. British Columbia Ministry of Health. Schedule of Fees For the Laboratory Services Outpatient: Payment Schedule [Internet]. 2017. [cited 2019 February 15]. Available from: https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/laboratory-services/laboratory_services_-_schedule_of_fees.pdf.
9. Ministry of Health and Long Term Care. Ontario Schedule of Benefits Physician Services Under the Health Insurance Act [Internet]. 2015. [cited 2018 December 12]. Available from: <http://www.health.gov.on.ca/en/pro/programs/ohip/sob/>.
10. Novartis Pharmaceuticals Corporation. Survey of Canadian Physicians Regarding Treatment Utilization and Frequency of Healthcare Services in Women Receiving First- or Second-Line Treatment for HR+/HER2- Advanced Breast Cancer. Brookline, MA: Policy Analysis Inc., July 2019.
11. National Institute for Health and Care Excellence. Ribociclib in combination with endocrine therapy and goserelin for previously untreated hormone receptor-positive, HER2-negative advanced breast cancer in premenopausal women (ID1307) [Internet]. 2018. [cited 2020 January 20]. Available from: <https://www.nice.org.uk/guidance/indevelopment/gid-ta10261>.