CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ribociclib (Kisqali) for Metastatic Breast Cancer

April 18, 2018

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding ribociclib (Kisqali) for advanced or metastatic breast cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding ribociclib (Kisqali) for advanced or metastatic breast cancer conducted by the Breast Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on ribociclib (Kisqali) for advanced or metastatic breast cancer, a summary of submitted Provincial Advisory Group Input on ribociclib (Kisqali) for advanced or metastatic breast cancer, and a summary of submitted Registered Clinician Input on ribociclib (Kisqali) for advanced or metastatic breast cancer, are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

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

Ribociclib is a selective cyclin-dependent kinase inhibitor, a class of drugs that help slow the progression of cancer by inhibiting two proteins called cyclin-dependent kinase 4 and 6 (CDK4/6). Ribociclib has a Health Canada indication that reflects the requested patient population for reimbursement. Health Canada has issued marketing authorisation for ribociclib in combination with letrozole for the treatment of postmenopausal women with hormone receptor HR-positive, HER2-negative ABC, as an initial endocrine-based therapy.

The recommended dose is 600 mg (3 x 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days. Ribociclib should be co-administered with letrozole 2.5 mg taken once daily throughout the 28-day cycle.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One randomized controlled trial was identified that met the eligibility criteria of the systematic review. MONALEESA-2 is an ongoing, international, multi-centred, phase 3, double-blind, placebo-controlled trial evaluating the efficacy and safety of ribociclib in combination with letrozole as first-line treatment for ABC.[1]

The trial randomized 668 patients; 334 were allocated to ribociclib-letrozole and 334 were allocated to placebo-letrozole. No treatment crossover was permitted. Women enrolled were post-menopausal, and had HR-positive, HER2-negative, locally advanced or metastatic breast cancer not amenable to curative treatment, with no previous systemic

therapy for their advanced disease, and an ECOG performance status of 0 or 1. Randomization was 1:1 and stratified according to the presence or absence of liver and lung metastases.

The primary outcome of the trial was progression-free survival by local investigator assessment (PFS by INV), according to RECIST version 1.1. Secondary outcomes included overall survival (OS), overall response rate (ORR), clinical benefit rate (CBR), health-related quality of life (QOL), and safety. A blinded independent central review (BICR) analysis of PFS was also performed and considered a supportive analysis.

The baseline characteristics of patients were well balanced between the two treatment groups. Most patients were treated at trial sites in Europe (44.3%) and North America (34.3%), with fewer patients treated in Asia (10.2%).[2] The median age was 62 years, with 44.2% of patients aged 65 and older.[2] The majority of patients were white (82.2%), had stage IV disease (99.4%), and a disease-free interval of ≥24 months (59.4%). Approximately one third (34%) of patients had de novo ABC. The most common sites of metastases were bone (any: 73.4%; only: 22%) and visceral (58.8%; lung and/or liver only: 55.8%), and approximately one third (34%) of patients had three or more metastatic sites. The percentages of patients previously treated in the neoadjuvant or adjuvant setting with endocrine therapy and chemotherapy were 51.8% and 43.6%, respectively.

Highlights of the key outcomes of the MONALEESA-2 trial are presented in Table 1.

Table 1: Highlights of key outcomes in the included MONALEESA-2 trial.

Efficacy Outcomes	**MONALEESA-2**			
Treatment Groups	**Ribociclib + letrozole (n=334)**	**Placebo + letrozole (n=334)**	**Ribociclib + letrozole (n=334)**	**Placebo + letrozole (n=334)**
Analysis	1st interim analysis[1]		2nd updated analysis[3]	
Data cut-off date	January 29, 2016		January 2, 2017	
Median follow-up in months	15.3		26.4	
Patients remaining on treatment, n (%)	195 (58.4)	131 (39.2)	154 (46.1)	88 (26.3)
Primary Outcome – PFS by investigator assessment				
No. PFS events (%)	93 (27.8)[2]	150 (44.9)[2]	140 (41.9)	205 (61.7)
Median PFS, months (95% CI)	Not reached (19.3-not reached)	14.7 (13.0-16.5)	25.3 (23.0-30.3)	16 (13.4-18.2)
HR* (95% CI, p-value)	0.56 (0.43-0.72; $p=3.29 \times 10^{-6}$)		0.57 (0.46-0.70; $p=9.63 \times 10^{-8}$)	
Key Secondary Outcomes				
ORR				
No. of patients with CR and PR	136	92	142	96
%, (95% CI)	40.7 (35.4-46.0)	27.5 (22.8-32.3)	42.5 (37.2-47.8)	28.7 (23.9-33.6)
OS				
No. deaths (%)	23 (6.9)	20 (6.0)	50 (15.0)	66 (19.8)
Median OS, months (95% CI)	NE	NE	Not reached	33 (33-not reached)
HR* (95% CI, p-value)	1.13 (0.62-2.06; p=0.653)[2,4]		0.75 (0.52-1.08; p=0.059)	
QOL				
Assessment of mean changes from baseline demonstrated no clinically meaningful differences between the treatment groups in any of the EORTC QLQ-C30 and B23 scale scores at any time point (that is, no difference met the MCID threshold of ≥10%).[5] The estimated mean difference in changes in global health status/QOL scale score between the treatment groups was -1.5 (95% CI, -4.0-1.0).[2] Time-to-deterioration of the global health status/QOL score by at least 10% was also similar between the treatment groups (HR=0.94, 95% CI, 0.72-1.24).[5]				

Efficacy Outcomes	MONALEESA-2			
Harms Outcomes, n (%)	1st interim analysis[1,a]		Updated safety analysis[3,b]	
AE (any grade)	329 (98.5)	320 (97.0)	331 (99.1)	322 (97.6)
Grade ≥3	271 (81.2)	108 (32.7)	288 (86.3)	123 (37.3)
SAE	71 (21.3)	39 (11.8)	85 (25.4)[4]	51 (15.5)[4]
Discontinuation due to AE	25 (7.5)[6]	7 (2.1)[6]	NR	NR

Abbreviations: AE - adverse events; **CI -** confidence interval; **CR -** complete response; **EORTC QLQ** - European Organization for Research and Treatment of Cancer's Core Quality of Life Questionnaire (**C30)** and Breast Cancer Specific Questionnaire **(BR23); HR -** hazard ratio, **MCID** – minimal clinically important difference; **NE** – not estimable; **NR** - not reported, **OR -** odds ratio; **ORR -** overall response rate; **OS** - overall survival, **PFS -** progression-free survival; **PR** – partial response; **QOL** -health-related quality of life; **SAE** - serious adverse event.

Notes:
* HR < 1 favours ribociclib-letrozole.
[a] All-cause AE reported in at least 15% of patients in the safety population (n=664); data cut-off date of January 29, 2016.
[b] All-cause AE reported in at least 20% of patients in the safety population; data cut-off date of January 4, 2017, which provides an additional 11 months of follow-up.

The trial met its primary outcome (crossed the pre-specified boundary for superiority) and demonstrated a statistically significant improvement in PFS by INV in the ribociclib-letrozole treatment group after a median follow-up of 15.3 months;[1] median PFS was not reached in the ribociclib-letrozole group and was 14.7 months in the placebo-letrozole group (hazard ratio, HR=0.56, 95% CI, 0.43-0.72; p-value=3.29×10^{-6}). The updated analysis of PFS by INV,[3] which was based on an additional 11 months of follow-up, showed the PFS benefit was sustained, and ribociclib-letrozole improved PFS by 9.3 months over placebo-letrozole (HR=0.57, 95% CI, 0.46-0.70; p-value=9.63×10^{-8}). The BICR analyses performed at both time points showed similar results. Tumour response outcomes, including ORR and CBR, were also consistently higher in the ribociclib-letrozole treatment group relative to placebo-letrozole. At the latest data cut-off, OS data remained immature with 15% and 19.8% of deaths in the ribociclib-letrozole and placebo-letrozole groups, respectively. Median OS was not reached in the ribociclib-letrozole group and 33 months in the placebo-letrozole group (HR=0.75, 95% CI, 0.52-1.08; p-value=0.059).[3] For QOL, assessment of EORTC QLQ-C30 and B23 scale scores overtime indicated no clinically meaningful differences between the treatment groups in mean changes from baseline or in the time-to-deterioration of scores from baseline.[5]

The incidence of adverse events (AEs) was similar between the treatment groups, with the majority of AEs being low grade. The AEs (any grade) occurring more frequently in the ribociclib-letrozole treatment group (vs. placebo-letrozole) included neutropenia (74.3% vs. 5.2%), nausea (51.5% vs. 28.5%), diarrhea (35% vs. 22.1%), alopecia (33.2% vs. 15.5%), leucopenia (32.9% vs. 3.9%), vomiting (29.3% vs. 15.5%), anemia (18.6% vs. 4.5%), increased alanine aminotransferase (ALT, 15.6% vs. 3.9%), and increased aspartate aminotransferase (AST, 15% vs. 3.6%).[1] Treatment interruptions, dose reductions, and treatment discontinuations due to AEs were all higher in the ribociclib-letrozole treatment group (vs. placebo-letrozole) and occurred in 68% (vs. 13.3%),[6] 50.6% (vs. 4.2%), and 7.5% (vs. 2.1%) of patients, respectively.

Grade 3 or 4 AEs occurred in substantially more patients treated with ribociclib-letrozole compared to patients treated with placebo-letrozole (32.7%); the majority of higher grade events in the ribociclib group were attributable to neutropenia (59.3%). The frequency of serious AEs (SAEs)[7] was also higher in the ribociclib-letrozole group (21.3%) compared to placebo-letrozole (11.8%); 7.5% and 1.5% of these events, respectively, were related to study treatment.

Limitations

Overall, the MONALEESA-2 trial was well-conducted. The randomization procedure, method of allocation concealment, and double-blind design were carried out appropriately. The treatment groups were well balanced for important baseline prognostic and patient characteristics, and length of time on treatment was also similar between the groups. There was transparent reporting of the disposition of patients through the trial, and outcome analyses were performed according to the intent-to-treat principle.

The superiority of ribociclib-letrozole demonstrated at interim analysis was based on crossing a stringent threshold of statistical significance (hazard ratio ≤0.57; p-value of 1.29 $x10^{-5}$). The interim results are likely robust considering the number of PFS events informing the analysis (80%); as much lower event rates are typically associated with overestimating treatment effects.[8] It is possible, however, that the higher incidence of neutropenia in the ribociclib-letrozole treatment group may have introduced bias into the investigator assessment of PFS (in favour of ribociclib-letrozole). The effect of this bias on the results obtained is likely minimal, however, since the BICR assessment reported PFS findings of similar magnitude.

The statistical analysis plan (SAP) of the trial specified the number of efficacy analyses to be performed of the primary outcome and the key secondary outcome, and used statistical tests to control for the probability of type 1 error that arises from multiple comparisons or "looks" at the trial data. The purpose of these statistical tests is to preserve the overall significance level across the number of planned, specified analyses and the overall power of the trial.[9] In the MONALEESA-2 trial, however, there were at least three analyses performed of the PFS data while the SAP only specified two analyses; analyses were performed on January 29, 2016,[1] June 22, 2016,[4] and January 2, 2017.[3] This is a limitation of the trial, since it is unknown what informed the decision to look at the data at additional time points. Undertaking unplanned interim analyses increases the risk of type 1 error, and consequently, can lead to exaggeration of treatment effects.[9] Therefore, the magnitude of the treatment estimates obtained should be interpreted with some level of caution.

The assessment of patient-reported QOL is limited,[5] and therefore as currently presented, may not fully capture the QOL experience of all patients in the trial. At many assessment time points patient compliance in completing questionnaires was low (missing data), which can bias findings since there are likely systematic differences in the characteristics of patients who complete and don't complete questionnaires. Further, the QOL results were only available in poster form, and therefore have not been fully peer-reviewed, as these sources selectively reported QOL outcomes.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

Two patient advocacy groups, Rethink Breast Cancer (Rethink) and Canadian Breast Cancer Network (CBCN), provided input on ribociclib for advances o metastatic breast cancer.

From a patient's perspective, managing a diagnosis of metastatic breast cancer is challenging, as current treatment options for metastatic breast cancer are only effective at prolonging progression-free disease, and most cases of advanced disease

will progress and symptoms will worsen. Rethink and CBCN indicated that the many side effects of metastatic breast cancer represent a significant or debilitating impact (both physical and social) on patients' and caregivers' quality of life. Rethink and CBCN reported that bone pain, insomnia, fatigue, muscle weakness, shortness of breath, nausea, and loss of appetite were the most common symptoms experienced as a result of breast cancer. Respondents indicated that ability to work, ability to perform household chores, ability to travel and pursue personal hobbies and interests were also impacted by the disease.

Respondents reported receiving a number of treatments, such as palbociclib, letrozole, capecitabine, paclitaxel, fulvestrant, exemestane, among others. Both Rethink and CBCN reported that current treatment options and effectiveness vary among type of cancer, location of cancer, and how symptoms are experienced. Respondents expressed concerns with the side effects and tolerability of traditional chemotherapy regimens. According to Rethink and CBCN, patients' expectations for the new treatment under review are the following: (1) to control the disease, (2) reduce symptoms, and (3) to improve on quality of life. Respondents who have experience with ribociclib reported that the treatment helped to stabilize and control their disease. Respondents also commented on the ease of taking the drug orally at home and appreciated the reduced travel requirements for treatment with ribociclib, and that the side effects were minimal and tolerable.

Provincial Advisory Group (PAG) Input

Input was obtained from the all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact implementation of ribociclib in combination with letrozole:

Clinical factors:

- Generalizability of data to use ribociclib in combination with other aromatase inhibitors
- Monthly monitoring and blood work for neutropenia, which is not required with letrozole monotherapy

Economic factors:

- Large number of patients eligible for treatment
- Cost effectiveness of add-on treatment of a new, high cost, drug

Registered Clinician Input

One joint submitting from three medical oncologists was provided.

The medical oncologists providing input noted that ribociclib plus letrozole compared to letrozole alone improved progression-free survival. However, it was noted that there are added toxicities of ribociclib not seen with letrozole alone. Clinicians noted that the eligible patient population, key benefits and harms, and sequencing of ribociclib would be similar to the pCODR review of palbociclib for HR- HER2- advanced or metastatic breast cancer. However, there is no direct evidence of ribociclib versus palbociclib.

Summary of Supplemental Questions

- Critical appraisal of the Manufacturer's submitted network meta-analysis (NMA) comparing endocrine-based therapies as first-line treatment in post-menopausal women with HR-positive and HER2-negative ABC.

The Manufacturer submitted a NMA comparing ribociclib-letrozole to other available endocrine-based therapies as first-line treatment in post-menopausal women with HR-positive and HER2-negative ABC. Results of the NMA have been published (conference poster) for the primary outcome of PFS,[10] and were critically appraised by the pCODR Methods Team according to the recommendations of the ISPOR Task Force on Indirect Treatment Comparisons.[11] The methods used to perform the systematic review informing the NMA were, for the most part, clear and comprehensive. However, it is possible that not all relevant trials were included. For an NMA to be feasible, the authors assumed equivalence of letrozole and anastrozole, combining these treatments into an aromatase inhibitors (AI) monotherapy treatment group. The NMA included five trials and five treatments available for comparison: AI monotherapy, ribociclib plus AI, palbociclib plus AI, fulvestrant 250mg plus AI, and fulvestrant 500mg. The patient populations of the trials aligned with the target population of this review (HER2-status, stage of disease, and first-line treatment of ABC); however, variation in the distribution of important baseline patient characteristics (treatment effect modifiers) was apparent and there was a substantial amount of missing data for other important variables. Considering these limitations, it is questionable whether it was appropriate to deem the trials similar enough to be compared in a NMA. Heterogeneity could not be explored using meta-regression analyses due to the small number of included trials, and therefore, unadjusted analysis results were reported based on a fixed effects analysis. The results of the NMA primary analysis indicated longer PFS with ribociclib plus AI, palbociclib plus AI, and fulvestrant compared to AI monotherapy, and no difference in PFS between ribociclib plus AI and palbociclib plus AI. Since the primary analysis did not adjust for differences between trials in important treatment effect modifiers, it is likely that the treatment effect estimates obtained in the NMA are biased and not solely due to the effects of the treatments examined, and therefore, should be interpreted with caution.

Refer to section 7.1 for the complete critical appraisal of the NMA.

- Critical appraisal of the Manufacturer's submitted indirect treatment comparison (ITC) and matching-adjusted indirect treatment comparison (MAIC) of ribociclib-letrozole and palbociclib-letrozole as first-line treatment in post-menopausal women with HR-positive and HER2-negative ABC.

The Manufacturer submitted an ITC and MAIC comparing ribociclib-letrozole to palbociclib-letrozole as first-line treatment in post-menopausal women with HR-positive and HER2-negative ABC. Results of the ITC and MAIC have been published (conference poster) for the primary outcome of PFS, OS and grade 3/4 AE,[12] and were critically appraised by the pCODR Methods Team according to the recommendations of the IPSOR Task Force on Indirect Treatment Comparisons and best practice principles for MAIC.[11,13] Very little information was reported on the systematic review that was performed to identify trials for the ITC and MAIC, and therefore, it is unclear how many treatments (and thus trials) were considered and excluded from the analyses. The scope of the primary analysis of PFS was limited to two trials and one treatment comparator: palbociclib-letrozole; therefore, the analyses did not address the relative efficacy of ribociclib-letrozole to other available treatments. The results of the ITC and MAIC were consistent, and showed treatment effect estimates that favoured ribociclib-letrozole over palbociclib-letrozole for PFS, however the difference between treatments was not statistically significant. The ITC demonstrated the risk of grade 3/4 AEs was significantly lower with placebo-letrozole compared to either targeted combination therapy. The risk of grade 3/4 AEs marginally favoured ribociclib-letrozole compared to palbociclib-letrozole. The pCODR Methods Team considered the internal validity of the PFS analysis of the ITC and MAIC to be adequate. This judgement

was based on the low risk of bias associated with the individual trials, the similarity of the trials being compared, a perceived low risk of confounding of the treatment effect (via imbalances in known treatment effect modifiers between trials), use of analysis techniques that comply with best practice, and the consistency of the results (treatment effect) obtained by the two methods of analysis. The ITC and MAIC of OS had a number of limitations and therefore the results should be interpreted with caution.

Refer to section 7.2 for the complete critical appraisal of the ITC and MAIC.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for ribociclib for advanced or metastatic breast cancer.

Domain	Factor	Evidence from the MONALEESA-2 trial[1]	Generalizability Question	CGP Assessment of Generalizability
Population	ECOG PS	Patients with an ECOG PS of 2 or greater were excluded. ECOG 0: n=405/668 (61%) ECOG 1: n= 261/668(39%)	Do the trial results apply to patients with an ECOG PS of 2 or greater? If so, why?	Most patients in clinical practice will have an ECOG PS of 0 or 1. The benefit for patients with ECOG 2 cannot be concluded, however it would be reasonable to expand combination therapy to patients with a good performance status, based on clinical experience and the manageable side-effect profile.
	Disease stage	Most patients in the trial had stage IV disease (versus stage III). Stage III: n=4/668 (<1%) Stage IV: n=664/668 (99%)	Is this representative of how patients present in Canadian practice? Does this limit the interpretation of the trial results to stage IV patients?	Interpretation of the trial results applies to metastatic disease (stage IV). In Canadian practice, the majority of patients with unresectable disease are metastatic.
	Brain metastases	Patients with brain metastases were excluded.	Do the trial results apply to patients with active brain metastases? If so, why?	While there is no evidence to support the use of the combination in patients with active or uncontrolled brain metastasis, it may be reasonable to expand combination therapy to patients with treated and stable CNS disease, based on the favourable side-effect profile and potential long-term OS in this population.

Domain	Factor	Evidence from the MONALEESA-2 trial[1]	Generalizability Question	CGP Assessment of Generalizability
	Time since progression (disease-free interval)	Patients who relapsed within 12 months of completion of neo (adjuvant) therapy were excluded from the MONALEESA-2 trial.	Are the results of this subgroup likely valid? If so, does this finding limit the interpretation of the trial results to patients with a disease interval >12 months?	There are no data to support use of combination ribociclib-letrozole in this population. This population likely has a poor response to further endocrine-based therapy.
	De novo disease	There were 34% (n=227/668) of patients who presented with de novo advanced/metastatic disease (who had not received any prior systemic therapy). At first interim analysis, the treatment effect in this patient subgroup was considered statistically significant (HR=0.45, 95% CI, 0.27-0.75).	Do the trial results apply to patients with de novo disease? If so, why?	The proportion of patients with de novo disease in the trial does not represent the typical population of women with advanced/metastatic breast cancer in Canada. Theoretically, the fact that patients had received no prior chemotherapy could have enhanced the benefit seen with targeted therapy. However, the CGP are unable to comment further.
	Organ dysfunction	The trial limited eligibility to patients with adequate bone marrow and organ function; and excluded patients with a history of inflammatory breast cancer, cardiac disease or dysfunction*, and impaired gastrointestinal function that altered drug absorption.	Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	It may not be reasonable to exclude patients with stable cardiac disease, who may otherwise benefit from combination therapy. In addition, patients with relapsed HR-positive inflammatory breast cancer could also expect clinical benefit with combination therapy. The CGP feels it is reasonable to exclude organ/marrow dysfunction and malabsorption, which would interfere with safe delivery of ribociclib. This issue would be generalizable to patient populations, including the Canadian population.
	Biomarkers	All included patients were HR-positive (100%, ER+ or PR+), and all but two patients were HER2-negative (99.7%). At first interim analysis, the treatment effect in the subgroup of patients who were both ER+/PR+ was considered statistically significant (HR=0.62, 95% CI, 0.46-0.82).	Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?	The CGP feels that these are reasonable biomarkers and inclusion criteria, based on available evidence. They would also be reasonable effect modifiers (i.e. ER+ positive would be more likely to respond to endocrine therapy). There is no evidence to support a clinically meaningful benefit in HER2+ patients at this time, and therefore use of ribociclib-

Domain	Factor	Evidence from the MONALEESA-2 trial[1]	Generalizability Question	CGP Assessment of Generalizability
				letrozole in this patient population cannot be endorsed.
Intervention	Treatment Intent	The intent of treatment in the trial was palliative (i.e. non-curative).	Are the results of the treatment generalizable to an alternative treatment intent? (i.e., if the trial is palliative in intent, could the therapy also be used in the adjuvant setting or vice versa?)	While the CGP acknowledges ongoing clinical trials in the adjuvant setting (i.e. earLEE-1[14] and earLEE-2[15]), there is insufficient evidence to support this indication.
Comparator	Combination with AI	Placebo (oral once daily for three weeks, one week off in 28-day cycle) plus letrozole (oral once daily, 2.5mg tablet, on a continuous schedule). Various AI are available for initial treatment of HR-positive, HER2-negative ABC. These include anastrozole, exemestane, and letrozole. PAG noted that the MONALEESA-2 trial compared ribociclib-letrozole to letrozole alone. PAG is seeking information on combining ribociclib with other AI.	Are the findings of this trial limited to letrozole, or are they generalizable to ribociclib in combination with other endocrine therapies? Why or why not?	Although the CGP were of the opinion that the three available AIs (anastrozole, exemestane and letrozole) have similar activity, direct comparisons and toxicity data for other combinations are lacking. Unlike palbociclib, there are no available data supporting the use of ribociclib in combination with other endocrine therapies. However, the CGP felt the combination of ribociclib with anastrozole (another non-steroidal AI) would be a reasonable combination in those patients intolerant to letrozole. There are no data to support combination therapy with tamoxifen, fulvestrant, or exemestane. The combination of ribociclib and fulvestrant is being evaluated in the MONALEESA-3 trial.[16,17]
	Standard of care in this setting is endocrine therapy.	The Manufacturer submitted an ITC and MAIC comparing ribociclib-letrozole to palbociclib-letrozole; and a NMA comparing ribociclib-letrozole to: AI (letrozole or anastrozole) monotherapy, palbociclib plus AI, fulvestrant 250mg plus AI, fulvestrant 500mg, and chemotherapy. Refer to the CGP interpretation in section 1.2.4 for more information.	Are the findings of this trial limited to letrozole, or are they generalizable other endocrine therapies? Why or why not?	According to the CGP there is currently no standard treatment approach in the first-line treatment of post-menopausal women with HR-positive and HER2-negative ABC. The sequencing of endocrine agents in the metastatic setting remains a topic of debate. Relevant comparators to ribociclib-letrozole currently include single agent endocrine therapies (i.e. anastrozole, letrozole, exemestane, tamoxifen), or the combination of palbociclib-letrozole, which is currently

Domain	Factor	Evidence from the MONALEESA-2 trial[1]	Generalizability Question	CGP Assessment of Generalizability
				not reimbursed in most provinces. The most relevant comparator is palbociclib-letrozole (i.e. same use of letrozole, and similar mechanism of action between palbociclib and ribociclib). Chemotherapy is usually reserved for post-endocrine therapy failure or for rapid control of a visceral crisis. Please refer to the CGP interpretation in section 1.2.4 for more information on the ITC, MAIC and NMA.
Outcomes	Short-term survival data	Data were deemed immature at the first and second interim analyses of OS. At the second, most recent interim analysis,[3] median follow-up time was 26.4 months and the number of deaths were 50 (15%) and 68 (19.8%) in the ribociclib-letrozole and placebo-letrozole groups, respectively (median OS was not reached vs. 33 months; HR=0.75 (0.52-1.08; p=0.059).	Is OS at just over two years reflective of longer-term survival? Why or why not?	PFS is an established and well agreed-upon primary endpoint, due to the prolonged expected survival of hormone sensitive, HER2-negative ABC patients.
Setting	Trial centres	The trial was conducted in 223 sites in 29 countries, including: Canada (8 sites, n=16), Australia (n=16), Austria (n=11), Argentina (n=6), Belgium (n=15), Brazil (n=8), Czech Republic (n=19), Denmark (n=12), Finland (n=3), France (n=43), Germany (n=55), Hungary (n=12), Ireland (n=4), Israel (n=32), Italy (n=32), Norway (n=9), Russia (n=11), South Africa (n=2), Korea (n=9), Singapore (n=9), Spain (n=44), Sweden (n=9), Taiwan (n=19), Thailand (n=4), Turkey (n=12), UK (n=4), and USA (n=213).[2]	Do the trial results apply to patients from Canadian centres? Are there any known differences in practice patterns between the countries listed and Canada?	Overall, most patients were from the US and Western Europe, where practice patterns are similar to Canada. However, differences in practice patterns may underlie the high number of de novo metastatic cases included in the MONALEESA-2 trial.

Abbreviations: ABC = advanced or metastatic breast cancer; **AI** – aromatase inhibitors; **CGP** – Clinical Guidance Panel; **CI** – confidence interval; **ECOG** - Eastern Cooperative Oncology Group; **ER** - estrogen receptor positive; **HER2** - human epidermal growth factor receptor 2; **HR** – hazard ratio; **ITC** – indirect treatment comparison; **MAIC** – matching adjusted indirect treatment comparison; **NMA** – network meta-analysis; **PAG** – Provincial Advisory Group; **OS** – overall survival; **PFS** – progression-free survival; **PS** – performance status; **vs.** - versus.

Notes:

* Patient has active cardiac disease or a history of cardiac dysfunction including any of the following:[18]
  - · History of angina pectoris, symptomatic pericarditis, or myocardial infarction within12 months prior to study entry
  - · History of documented congestive heart failure (New York Heart Association functional classification III-IV)
  - · Documented cardiomyopathy

Domain	Factor	Evidence from the MONALEESA-2 trial[1]	Generalizability Question	CGP Assessment of Generalizability
· Patient has a Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO). · History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality in the previous 12 months. · On screening, any of the following cardiac parameters: bradycardia (heart rate < 50 at rest), tachycardia (heart rate > 90 at rest), PR interval > 220 msec, QRS interval >109 msec, or QTcF >450 msec. · Systolic blood pressure >160 or <90 mmHg.				

1.2.4 Interpretation

Burden of Illness and Need

Breast cancer remains the most common malignancy diagnosed in Canadian women, with a projection of 26,300 new cases and 5000 deaths in 2017.[19] Approximately one in eight Canadian women will be diagnosed with breast cancer in their lifetime. This represents a large burden of disease within the Canadian population.

A proportion of these patients are diagnosed with recurrent or de novo metastatic disease. Unfortunately ABC remains incurable, and is treated systemically with palliative intent. In the setting of metastatic disease, median life expectancy is approximately two to three years.[20]

The majority (75%) of ABC is HR-positive,[1] allowing for administration of first-line palliative estrogen-based therapy. Endocrine therapy is often chosen based on its ease of use, favourable side effect profile, and ability to control disease for extended periods of time. However, most endocrine-sensitive breast cancers inevitably develop acquired resistance to hormone-based therapy, necessitating a change in palliative treatment approach. In addition, a small proportion of patients with HR-positive disease at initial presentation do not respond to first-line endocrine therapy, and are considered to have primary endocrine resistance. The CGP agreed with the clinicians providing input to this submission, that there is an urgent need for more effective and durable first-line therapies in the metastatic setting.

Until recently, endocrine therapy options have remained static, with little significant advancement in the treatment landscape. Fortunately, this has changed with the development of CDK inhibitors, small molecule kinase inhibitors, which target the cellular replication pathway, and complement the effects of endocrine agents currently in clinical use. CDK inhibition represents a novel and important advancement in the first-line management of HR-positive, HER2 negative metastatic breast cancer.

Effectiveness

MONALEESA-2 is an ongoing, international, multi-centre, phase 3, double-blind, placebo-controlled randomized trial evaluating the efficacy and safety of ribociclib in combination with letrozole as first-line treatment for women with HR-positive, HER2-negative ABC.[1] This is the only phase 3 clinical trial available with mature PFS data, and is therefore the only direct trial discussed in these interpretations and conclusions. MONALEESA-2 involves 223 participating sites in 29 countries, including Canada (8 sites).[2] Therefore, results can be considered generalizable to the Canadian patient population. Patients were eligible for participation if they were post-menopausal, had HR-positive, HER2-negative ABC not amenable to curative therapy with measurable disease (or at least 1 lytic bone lesion), adequate performance status (ECOG 0-1) and adequate bone marrow and organ function. This is a typical clinical trial population considered for first-line endocrine therapy in the advanced/metastatic setting. However in clinical practice, it may be reasonable to consider offering therapy to patients with an ECOG PS of 0-2, due to the manageable side-effect profile of both endocrine therapy and CDK inhibitors. Patients were

excluded from the trial if they previously received a non-steroidal AI within 12 months of enrollment, or were previously treated with a CDK inhibitor. Participants were also excluded if they had inflammatory breast cancer, central nervous system (CNS) disease, a history of cardiac dysfunction, or concern for malabsorption syndromes. These are common exclusion criteria in the clinical trial setting, and are consistent across similar first-line metastatic CDK inhibitor RCTs. We assume that exclusion of inflammatory breast cancer refers only to patients presenting with de novo locally advanced and not metastatic disease, where more rapid control of disease is required. In addition, the term 'cardiac dysfunction' is very broad, therefore it may not be clinically reasonable to exclude patients with stable cardiac disease from ribociclib therapy. Finally, patients with treated and stable CNS disease may also benefit from combination ribociclib-letrozole therapy for management of systemic metastasis, and so consideration should also be given to this patient population.

Participants were randomized to oral ribociclib 600 mg or placebo once daily for three weeks followed by one week of rest every 28 day cycle, in combination with letrozole 2.5 mg once daily. This treatment schedule is similar to that described in the PALOMA-2 trial.[21] Treatment continued until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. The primary outcome measure was PFS by INV; and the secondary measures were OS, ORR, CBR, safety, and QOL (based on patient questionnaires). Progression-free survival is an established and well agreed-upon primary endpoint in the breast cancer literature. It is often difficult to use OS as a primary endpoint in this population, in part due to the prolonged expected survival of metastatic, hormone sensitive, HER2-negative breast cancer patients, as well as the wide choice of therapies that are available to patients upon progression.

A total of 668 patients were randomized, 334 to the ribociclib-letrozole group, and 334 to the placebo-letrozole group.[1] Treatment groups were well-balanced, and the median duration of treatment was comparable between both arms (13 months in the ribociclib-letrozole group versus 12.4 months in the placebo-letrozole group). There was a statistically significant improvement in PFS by INV in the ribociclib-letrozole treatment group (95% CI, 19.3-not reached) versus the placebo-letrozole group (95% CI, 13.0-16.5 months); the HR was 0.56 (95% CI, 0.43-0.72; $p=3.29x10^{-6}$). It is important to note that the trial met its pre-specified boundary for superiority at first interim analysis. This represents both a statistical and clinically meaningful improvement in PFS. The magnitude of benefit was similar to that achieved in the PALOMA-1 and PALOMA-2 trials, which both investigated palbociclib in combination with letrozole.[21,22]

The updated second analysis of PFS by INV based on 345 PFS events showed a sustained benefit in the ribociclib-letrozole treatment group, after an additional 11 months of follow-up.[3] The median PFS by INV was 25.3 months in the ribociclib-letrozole group, compared to 16 months in the placebo-letrozole group, indicating a 9.3 month improvement in PFS with use of ribociclib–letrozole (HR= 0.57, 95% CI, 0.42-0.77; $p=9.63x10^{-8}$). Blinded independent assessment of PFS yielded similar HRs; however there was some discordance between assessments, possibly related to the subjective nature of bone lesion assessment.[2] It was not felt that this discordance between the different assessments biased efficacy results. In addition, the PFS benefit observed in the ribociclib-letrozole treatment group was consistent in all pre-specified patient subgroups. The estimated HRs amongst the various subgroups ranged from 0.39-0.69.[1] However, the subgroup analysis results should be interpreted with caution as they were exploratory and no adjustments were made to account for multiple comparisons. The OS data remained immature at both interim analyses, as clinically expected.

Tumor response outcomes were considerably higher in the ribociclib-letrozole treatment group at both analysis time points.[1,3] At first interim analysis, the ORR was 40.7% in the ribociclib-letrozole treatment group, compared with 27.5% in the placebo group, representing an absolute difference of 13.2%, ($p<0.001$).[1] The CBR was 79.2 % versus 72.8% in the ribociclib-letrozole versus placebo-

letrozole groups, respectively, representing an absolute difference of 6.4% (p=0.02).The corresponding ORR and CBR at the second updated analysis were similar.[3] Therefore, all secondary endpoints were concordant with the primary PFS benefit observed at both analysis time points.

Finally, the QOL outcome results were derived from the EORTC QLQ-C30 and B23 questionnaires.[5] No significant differences in health-related QOL measures between the two treatment groups were observed during the treatment phase of the trial. The estimated mean difference in changes in global health status/QOL scale score between the treatment groups was -1.5 (95% CI, -4.0-1.0). During treatment, overall QOL (global health status/QOL score) was maintained from baseline and was similar in both treatment groups. Global health status/QOL scores (the primary variable of interest), slightly improved numerically (increase in scores) from baseline in both treatment groups, and then declined (worsened) by the end of treatment. Patient compliance was high (greater than or equal to 90% compliance) up to cycle 19 and declined substantially thereafter, as patients did not complete questionnaires after disease progression. These data suggest that ribociclib compliance in the clinical setting would be reasonable. Overall, the CGP agreed that ribociclib-letrozole maintains QOL in this patient population and that the AEs of ribociclib combined with letrozole did not significantly impact overall QOL. The CGP considered the QOL observed in the trial was in line with patient group input for this submission. Patients expect that ribociclib will allow them to live with a better QOL than if they were to receive chemotherapy or other hormonal therapies with more significant toxicity profiles. The majority of patients with exposure to ribociclib reported that side effects were minimal and that their QOL, including productivity and ability to regain mobility and perform daily functioning, had improved on ribociclib.

In order to assess the comparative efficacy and effectiveness of ribociclib-letrozole to comparators, other than the comparator (placebo-letrozole) used in the MONALEESA-2 trial, the Submitter provided an ITC and MAIC of ribociclib-letrozole and palbociclib-letrozole;[12] as well as a NMA comparing endocrine-based therapies for the first-line treatment of post-menopausal women with HR-positive and HER2-negative ABC.[10]

The CGP noted that palbociclib-letrozole is the most relevant comparator to ribociclib-letrozole in this setting (i.e. same use of letrozole, and similar mechanism of action between palbociclib and ribociclib). The CGP acknowledged that the ITC and MAIC provided by the Submitter demonstrated treatment effect estimates that slightly favoured ribociclib-letrozole over palbociclib-letrozole for PFS and OS, but the results were not statistically significant.[12] The risk of grade 3/4 AEs was significantly lower with placebo-letrozole compared to either targeted combination therapy. The risk of grade 3/4 AEs marginally favoured ribociclib-letrozole compared to palbociclib-letrozole. The quality assessments performed by the pCODR Methods Team judged the credibility of the ITC and MAIC of PFS to be adequate, however, indicated that the analysis of OS was deemed exploratory (due to immature OS data and other limitations) and should be interpreted with caution. While the CGP noted that it seemed likely that similar benefits and side-effect profiles would be observed between ribociclib-letrozole and palbociclib-letrozole, the CGP cautioned against drawing conclusions on the magnitude of effect of ribociclib-letrozole compared with palbociclib-letrozole given the absence of more robust direct evidence from a randomized trial and absence of long term OS and QOL data. The CGP concluded that there is insufficient evidence to determine the comparative effectiveness and safety of ribociclib-letrozole compared to palbociclib-letrozole and therefore treatment availability, patient values and preferences, and clinical factors should guide treatment selection. Refer to section 7.2 for the complete critical appraisal of the ITC and MAIC.

The CGP noted that the submitted NMA included five trials and five treatments available for comparison: AI monotherapy, ribociclib plus AI, palbociclib plus AI, fulvestrant 250mg plus AI, and fulvestrant 500mg.[10] The results of the NMA primary analysis indicated longer PFS with ribociclib plus AI, palbociclib plus AI, and fulvestrant 500mg compared to AI monotherapy; superior PFS with

targeted combination therapy when compared to fulvestrant 250mg plus AI and fulvestrant 500mg; and no difference in PFS between ribociclib plus AI and palbociclib plus AI. However, the critical appraisal performed by the pCDOR Methods Team identified several limitations of the NMA and judged its overall credibility to be weak. One of the main limitations was the lack of adjustment for differences between trials in important treatment effect modifiers. Therefore, it is likely that the treatment effect estimates obtained in the NMA are biased and not solely due to the effects of the treatments examined, and therefore, should be interpreted with caution. The CGP concluded that there is insufficient evidence to determine the comparative effectiveness and safety of endocrine therapies provided in the NMA. Hence treatment availability, patient values and preferences, and clinical factors should guide treatment selection. Refer to section 7.1 for the complete critical appraisal of the NMA.

Safety

Safety analysis results from the first and second analyses of the MONALEESA-2 trial were similar.[1,3] Adverse events of any grade occurred in 98.5% of ribociclib-treated patients, compared to 99.1% of placebo-treated patients.[1] The majority of AEs were low grade. However, 'any-grade' AEs occurring more frequently in the ribociclib-letrozole treatment group included neutropenia (74.3% versus 5.2%), nausea (51.5% versus 28.5%), diarrhea (35% versus 22.1%), alopecia (33.2% versus 50.5%), leukopenia (32.9% versus 3.9%), vomiting (29.3% versus 50.3%), anemia (18.56% versus 4.5%), increased ALT (50.6% versus 3.9%), and increased AST (50% versus 3.6%). These rates are comparable to other CDK inhibitors currently on the market. Treatment interruptions (68% vs. 13.3%), dose reductions (50.6% vs. 4.2%), and discontinuation (7.5% vs. 2.1%) due to AEs were all higher in the ribociclib-treated group. The frequencies of AEs are similar to those reported in the PALOMA-2 trial.[21]

There were more grade 3 and 4 AE in the ribociclib-treated arm (81.2%) compared to patients receiving letrozole alone (32.7%).[1] The majority of these events were attributed to neutropenia (59.3%). Dose interruptions were required in 49.7% of patients, and dose reductions in 31.1%. Most of these adjustments occurred early in the treatment phase, and treatment discontinuation was rare (<1% of patients).[6] Febrile neutropenia was reported in five patients receiving ribociclib (1.5%).[1] Based on previous experience with CDK inhibitors, neutropenia is a familiar and manageable side-effect of therapy, and trial data suggests that febrile neutropenia remains an uncommon complication of treatment. It is therefore expected that use of ribociclib in the clinical setting will require more frequent monitoring and laboratory investigations, when compared to use of endocrine therapy alone. However, breast oncologists are comfortable monitoring this treatment toxicity, based on experience with other myelosuppressive agents.

Serious adverse events were higher in the ribociclib arm (21.3% versus 11.8%).[7] However, only 7.5% (vs. 1.5%) of these events were related to study treatment. Ten deaths occurred during the treatment phase of trial, seven (2.1%) in the ribociclib treatment group and three (0.9%) in the placebo group.[1,3] Causes of death included underlying breast cancer (n=2) acute respiratory failure (n=2), pneumonia (n=1), sudden death (n=1), and death from unknown causes (n=1).[1,3] The reported sudden death was attributed to hypokalemia and prolongation in the QT interval,[1] related to prohibited concomitant medications. In clinical practice, use of prohibited concomitant medications is more likely to occur (i.e. strict trial protocol criteria are unlikely to be applied to the same degree). This could potentially be a cause of further SAEs in post-marketing surveillance.

Overall the CGP agreed with the clinicians providing input for this submission that although ribociclib has more toxicity than letrozole, ribociclib is considered to be overall well tolerated. Further, the CGP acknowledged patient advocacy input stating that the majority of patients with ribociclib exposure reported that ribociclib had a positive impact on their health and well-being with minimal and tolerable side effects.

1.3 Conclusions

The CGP concluded that **there is a net overall clinical benefit** with the combination of ribociclib-letrozole, compared to letrozole alone, in the treatment of post-menopausal women with HR-positive, HER2-negative, ABC who have not received prior treatment for metastatic disease. This is based on the results of a single RCT (MONALEESA-2).[1] Based on the first and second updated analysis of PFS, there is an approximate 9.3 month improvement with combination ribociclib-letrozole therapy, compared to letrozole therapy alone.[1,3]

The trial data on OS remains immature, however, it should be noted that subsequent OS analysis may be confounded by post-trial treatment administration, (particularly with use of palbociclib, which is currently Health Canada approved).

The CGP concluded that the safety and QOL profile of combination ribociclib-letrozole is acceptable and comparable to combination palbociclib-letrozole, with reasonable expectations for patient compliance. Combination therapy will require closer clinical monitoring when compared to use of endocrine therapy alone, however, the side effect profile is predictable and familiar to medical oncologists. Medical education and prophylactic treatment strategies will need to be developed in order to manage unexpected SAEs noted during post-marketing surveillance.

In making this conclusion the CGP also considered that:

- As the MONALEESA-2 trial only included patients with ECOG performance status 0-1, the CGP cannot conclude a net clinical benefit outside of this population. However, the CGP suggested that combination ribociclib-letrozole could be considered for patients with a good performance status, based on clinical experience with CDK inhibitors and the manageable side effect profile of this combination.

- While MONALEESA-2 studied only the combination of ribociclib with letrozole, the CGP supports consideration of the combination of ribociclib with alternate non–steroidal AI such as anastrozole in patients who are intolerant to letrozole. Endocrine therapies such as tamoxifen, exemestane and fulvestrant are sufficiently different from non-steroidal AI in pharmacology and mechanism of action, and clinical data combining these agents with ribociclib is non-existent or limited; consequently, the CGP does not support these combinations until the results of ongoing clinical trials are available.

- The MONALEESA-2 trial studied only the combination of ribociclib with letrozole in the first-line advanced/metastatic setting. Therefore, at this time the CGP cannot recommend this particular combination in second-line metastatic therapy, or in the (neo) adjuvant setting. The CGP acknowledges ongoing clinical trials in the adjuvant setting (earLEE-1 and earLEE-2).[14,15]

- The MONALEESA-2 trial excluded patients with CNS disease, inflammatory breast cancer, cardiac disease or dysfunction, and malabsorption syndromes. The CGP cautions against restricting combination ribociclib-letrozole therapy in patients with stable cardiac disease or treated/stable CNS disease, based on the favourable side-effect profile of therapy and possible long-term OS of these patients.

- The CGP acknowledges recent evidence showing similar benefits and side-effect profiles with combination palbociclib-letrozole therapy (PALOMA-2 and PALOMA-2).[21,22] However, there is insufficient evidence to demonstrate superiority of either ribociclib or palbociclib in this patient population, and the CGP cannot recommend one therapy over the other.

There is also insufficient evidence to support substituting palbociclib with ribociclib due to intolerance.

- Given the limitations identified in the submitted ITC, MAIC and NMA there is no reliable estimate of the comparative efficacy or effectiveness of ribociclib-letrozole to palbociclib-letrozole, or fulvestrant-anastrozole or fulvestrant monotherapy or chemotherapy. Hence, treatment availability, patient values and preferences, and clinical factors should guide treatment selection. (Refer to section 7 for the complete critical appraisal of the ITC, MAIC and NMA).

- As there is no direct evidence to support the addition of ribociclib to patients already receiving letrozole (or other AI) with stable disease, the CGP cannot make a firm recommendation at this time.

- Patients on the MONALEESA-2 trial discontinued combination therapy at the time of disease progression, measured using RECIST 1.1 criteria. Therefore, the CGP cannot recommend continuation of ribociclib for oligoprogression, due to lack of evidence.

- MONALEESA-2 excluded patients who relapsed <12 months after completion of adjuvant therapy. The CGP would be hesitant to support the use of ribociclib-letrozole in this patient population, due to lack of data. Similarly, patients who were resistant to AI therapy in the neoadjuvant setting would be unlikely to benefit from combination therapy in the metastatic setting, although the CGP acknowledges this question was not addressed in the trial.

- The CGP is unable to make evidence-based recommendations on the optimal sequencing of ribociclib-letrozole and everolimus-exemestane, nor comment on the cost-effectiveness of second-line therapy in the post-progression setting, due to lack of data.

- The CGP acknowledges that there are dose scheduling differences between ribociclib and letrozole, which may increase risk of patient medication error. For this reason, careful patient education and treatment monitoring will be required for safe administration of this combination therapy.

- Generalizing the MONALEESA-2 trial results to male patients might be reasonable. However, as males were not included in the trial, direct evidence is lacking at this time. It is unlikely that there will be trials specifically designed for this small group of patients and there is no biological rationale to assume that outcomes of ribociclib plus letrozole therapy would be different between male and female patients with HR-positive, HER2-negative advanced or metastatic breast cancer.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Breast Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Breast cancer remains the most common malignancy diagnosed in Canadian women, with a projected 26,300 new cases and 5000 deaths in 2017.[19] Approximately one in eight Canadian women will be diagnosed with breast cancer in their lifetime. A proportion of these patients are diagnosed with recurrent or de novo metastatic disease. Unfortunately advanced or metastatic breast cancer remains incurable, and is treated systemically with palliative intent. In the setting of metastatic disease, median life expectancy is approximately 2-3 years.[20]

The goals of palliative systemic therapy are threefold: to maintain or improve quality of life, to slow further progression of disease, and to prolong survival. Clinicians have several systemic treatment options available, depending on the histology, HR status, and HER2-neu receptor status of the disease. Patient factors, performance (functional) status, and patient preferences are also considered. Systemic options broadly include endocrine therapy, biologic/targeted therapies, and chemotherapy. These therapies are used in conjunction with bone modifying agents (e.g. bisphosphonates and RANK ligand inhibitors), radiation therapy, and supportive care (e.g. analgesics, antiemetics), depending on the clinical situation.

Approximately 75% of breast cancers over-express estrogen and/or progesterone hormone receptors.[1] In the absence of rapidly progressive disease or visceral crisis, endocrine-based therapy is often considered first-line palliative treatment in hormone receptor (HR)-positive, HER2 negative disease, based on its efficacy and favorable toxicity profile. Commonly used options include selective estrogen receptor modulators (e.g. tamoxifen or raloxifene), aromatase inhibitors (e.g. anastrozole, letrozole, and exemestane), selective estrogen receptor degraders (e.g. fulvestrant), and less commonly, progesterone agents (e.g. megestrol acetate). Unfortunately, most endocrine-sensitive breast cancers inevitably develop acquired resistance to hormone-based therapy, necessitating a change in palliative treatment approach. In addition, a small proportion of patients with HR-positive disease at initial presentation do not respond to first-line endocrine therapy, and are considered to have primary endocrine resistance. First-line endocrine therapy treatment failures have fueled research interest in better understanding intracellular pathways and mechanisms involved with both acquired and primary endocrine resistance, in order to circumvent these outcomes. Recent studies have expanded our knowledge related to intracellular signaling, allowing the development and usage of targeted agents such as everolimus, which acts on the mTOR signaling pathway.[23]

2.2 Accepted Clinical Practice

Currently, there is no standard treatment approach in the management of metastatic HR positive breast cancer. The sequencing of endocrine agents in the metastatic setting remains a topic of intense study and debate. Treatment algorithms are often chosen using a variety of factors, including: previous exposure to therapies in the adjuvant setting, duration between adjuvant therapy and diagnosis of metastatic disease, tempo of disease progression, location and involvement of tumour sites, clinical status and co-morbidities of the patient, individual preferences, and provincial treatment funding guidelines.

As previously discussed, advanced breast cancer invariably develops mechanisms of resistance to endocrine-based systemic therapy. One such mechanism involves constituent activation of the PI3K-Akt-mTOR signaling pathway.[24] Targeted agents such as everolimus have been developed to

block this signal transduction pathway, and have shown clinical progression free survival benefit in combination with exemestane (aromatase inhibitor) therapy.[23] Another signaling pathway involves aberrant dysregulation of the cell division cycle. Cellular replication involves a host of tightly regulated steps, all coordinated by specialized cell cycle signaling molecules. One family of cell cycle regulators include cyclin-dependent kinases (CDKs), a series of small molecule serine threonine kinase enzymes that combine with their associated cyclins to regulate the passage of cells through the growth and division cycle. Studies have uncovered multiple genetic mutations which activate these pathways, leading to uncontrolled growth and rapid division of malignant cells. Overcoming the inappropriate activation of CDKs has proven to be an additional therapeutic tool to limit progression of metastatic breast cancer.

Recently, palbociclib (Ibrance, Pfizer) has been developed to block the CDK 4/6 cyclinD pathway. Palbociclib is an oral, reversible small molecule inhibitor of cyclin dependent kinase 4/6, which prevents its association with cyclin D. This prevents the phosphorylation and subsequent inactivation of the retinoblastoma (Rb) protein, a key player in regulation of cell cycle progression, ultimately halting progression of cells through G1/S phase of the cell cycle.[25] A number of pre-clinical and clinical studies have demonstrated that the combination of palbociclib with either tamoxifen,[26] aromatase inhibitors[21,22] or fulvestrant[27] are able to overcome endocrine resistance, and improve progression free survival (PFS). In addition, the combination of palbociclib and endocrine therapy has a reasonable toxicity profile, especially when compared with standard chemotherapy.[21,22,27] In 2016, palbociclib received Notice of Compliance (approval) by Health Canada when used in combination with letrozole for treatment of HR-positive breast cancer. Expanded approval for use in combination with fulvestrant was subsequently granted in 2017, based on data from the PALOMA-3 clinical trial.[27]

Ribociclib (Kisqali, Novartis) is another oral, selective CDK 4/6 inhibitor with similar properties and indications for management of ER-positive ABC. Novartis applied for Notice of Compliance by Health Canada in May 2017, in combination with letrozole, based on interim results from the phase 3 MONALEESA-2 clinical trial.[1] A follow-up phase 3b open-label treatment trial is currently underway to collect additional safety and efficacy data.[28] This ongoing trial includes male participants. Additional phase 3 trials are currently underway to investigate the efficacy and tolerability of ribociclib in combination with fulvestrant[16,17] in both men and women, and for treatment of pre-menopausal women in combination with goserelin and either tamoxifen or aromatase inhibitor therapy.[29] Additional phase 3 trials are being planned to investigate the utility of ribociclib in combination with endocrine therapy in the adjuvant setting[14,15] in both men and women. The purpose of this review is to evaluate the benefit of combined ribociclib and endocrine therapy in the first-line management of HR-positive, HER2- negative ABC in the post-menopausal setting. This is the current United States Food and Drug Administration (FDA) approved indication.

2.3 Evidence-Based Considerations for a Funding Population

The evidence-based population suitable for consideration of combination ribociclib and letrozole for the first-line treatment of HR positive advanced breast cancer is similar to the population studied in the MONALEESA-2 clinical trial.[1] This population includes: post-menopausal women with HR-positive, HER2-neu negative invasive mammary carcinoma, first-line therapy in the advanced metastatic setting, adequate performance status (ECOG PS 0-1), and adequate bone marrow and organ function. In the study, women who had previously been exposed to CDK 4/6 inhibitors, endocrine therapy, or chemotherapy in the advanced setting were excluded. Women who had previously been exposed to endocrine therapy in the adjuvant setting were also eligible for therapy with ribociclib, if they relapsed more than 12 months after completion of adjuvant therapy.

2.4 Other Patient Populations in Whom the Drug May Be Used

Other patient populations may also derive benefit from therapy with ribociclib, especially those studied in the PALOMA series of palbociclib clinical trials, including pre-menopausal women and men. In addition, alternative combinations of endocrine therapy with ribociclib are also reasonable to evaluate for efficacy and toxicity. These include combining ribociclib with fulvestrant,[16,17] goserelin, aromatase inhibitors, or tamoxifen.[15,29] Finally, women enrolled in the adjuvant ribociclib phase III clinical trials [14,15] may also be derive benefit from combination therapy, however this remains to be proven.

Currently, there is no data to support use of ribociclib in the setting of HER2-neu positive disease, central nervous system metastasis, or in subsequent lines of therapy for advanced disease.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, Rethink Breast Cancer (Rethink) and Canadian Breast Cancer Network (CBCN), provided input on the Ribociclib (Kisqali) submission for the treatment of post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as an initial endocrine-based therapy.

CBCN conducted an on-going, online survey distributed to patients living with metastatic breast cancer (2017 survey). Patients were contacted through the membership databases of CBCN and other patient organizations. At the time of this submission, 157 metastatic patients participated in the survey with 65 patients identifying as being HR-positive. The survey questions were comprised of a combination of scoring options and free-form commentary.

CBCN in collaboration with Rethink conducted an online survey of metastatic breast cancer patients and caregivers in 2012 (2012 survey). Patients were contacted through the membership databases of CBCN and Rethink. Seventy-one patients and 16 caregivers participated in the survey. None of the patients who participated in this survey had experience with the treatment under review. Questions in the survey included a combination of scoring options and free-form commentary.

CBCN also conducted key informant interviews in September and October 2017 with two Canadian metastatic breast cancer patients living with HR-positive breast cancer that had direct experience with the treatment under review. A literature review of current studies and grey literature was also carried out by CBCN to identify issues and experiences that are commonly shared among many women living with breast cancer.

In addition, Rethink collected patient input from online surveys between September 25, 2017 and October 29, 2017. The survey asked questions about the impact of breast cancer on the lives of patients and the effect of current treatments. The survey also included questions directed to patients who had treatment experience with ribociclib. Potential responders were identified through the organizational mailing list, the Rethink Breast Cancer Young Women's Network, partner organizations as well as Facebook, Twitter, and the Breastcancer.org and Cancer Survivors Network online discussion boards. Fifteen patients completed the survey, of which 10 were from Canada (AB, BC, ON, and QB), and five were from the US. Of these patients, all have been diagnosed with HR-positive, HER2-negative advanced breast cancer and 14 are post-menopausal. Seven women have treatment experience with ribociclib and of those, five reported that they received ribociclib in combination with Femara (letrozole), and six reported they received other therapies before being treated with ribociclib.

Rethink asked patients through the survey if they would be willing to participate in a one-to-one interview to elaborate on their experience. Three women were interviewed by a Rethink Breast Cancer staff member. These interviews were conducted by telephone or email.

From a patient's perspective, managing a diagnosis of metastatic breast cancer is challenging, as current treatment options for metastatic breast cancer are only effective at prolonging progression-free disease, and most cases of advanced disease will progress and symptoms will worsen. Rethink and CBCN indicated that the many side effects of metastatic breast cancer represent a significant or debilitating impact (both physical and social) on patients' and caregivers' quality of life. Rethink and CBCN reported that bone pain, insomnia, fatigue, muscle weakness, shortness of breath, nausea, and loss of appetite were the most common symptoms experienced as a result of breast cancer. Respondents indicated that ability to work, ability to perform household chores, ability to travel and pursue personal hobbies and interests were also impacted by the disease.

Respondents reported receiving a number of treatments, such as palbociclib, letrozole, capecitabine, paclitaxel, fulvestrant, exemestane, among others. Both Rethink and CBCN reported that current treatment options and effectiveness vary among type of cancer, location of cancer, and how symptoms are experienced. Respondents expressed concerns with the side effects and tolerability of traditional chemotherapy regimens. According to Rethink and CBCN, patients' expectations for the new treatment under review are the following: (1) to control the disease, (2) reduce symptoms, and (3) to improve on quality of life. Respondents who have experience with ribociclib reported that the treatment helped to stabilize and control their disease. Respondents also commented on the ease of taking the drug orally at home and appreciated the reduced travel requirements for treatment with ribociclib, and that the side effects were minimal and tolerable.

Please see below for a summary of specific input received from Rethink and CBCN. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that were reported have also been reproduced according to the submission and have not been corrected.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients Have with HR-positive HER2-negative Advanced or Metastatic Breast Cancer

According to the 2012 Rethink and CBCN survey, current treatment options for HR-positive metastatic breast cancer are only effective at prolonging progression-free disease, and most cases of advanced disease will progress and symptoms will worsen. Both Rethink and CBCN indicated that patients with a diagnosis of metastatic breast cancer understand the limitations of current treatment options, and seek to live their remaining months and years with the best possible quality of life that they can achieve.

The diagnosis of advanced breast cancer, as well as the treatments that are used, impact both the social and physical well-being of a patient, thus impacting their quality of life. Both Rethink and CBCN reported from the 2012 survey how the disease presents itself through symptoms, how it progresses, and how it is experienced varies by patient. They also reported that many effects of metastatic breast cancer represent a significant or debilitating impact on patients' quality of life.

In the 2012 survey, patients were asked what physical impact cancer-related symptoms had on their quality of life. Below are the key responses that were reported by respondents:

- 54% of patients reported that fatigue resulted in a significant or debilitating impact, and 40% reported some or moderate impact
- 39% of patients reported that insomnia resulted in a significant or debilitating impact, and 46% reported some or moderate impact
- 37% of patients reported that pain resulted in a significant or debilitating impact, and 44% reported some or moderate impact

CBCN noted that these results were reinforced in their 2017 survey of metastatic patients. Through a preliminary analysis of the responses of 65 HR-positive patients, CBCN indicated that the key concerns listed by patients in the management of their disease are managing pain, starting treatment as early as possible following diagnosis, accessing hormone therapy and targeted therapies over chemotherapy, and managing the side effects of chemotherapy.

Rethink also reported from their 2017 patient survey that four patients reported that they were diagnosed in 2017, five in 2015-2016, two in 2013-2014, and four were diagnosed earlier. Patients

reported the symptoms they had experienced as a result of breast cancer: bone pain, reported by 75% of the 15 respondents, was the most common, followed by shortness of breath (50%), muscle weakness (33%), and loss of appetite (33%). Patients also reported on how the symptoms associated with breast cancer have impacted their lives on a scale of 1 (no impact) to 5 (significant impact). Respondents indicated that the greatest impact was on their ability to work and ability to travel, followed by ability to exercise and ability to perform household chores. The following table illustrates the breakdown by percentage values for the responses that were reported.

Impact of breast cancer symptoms on the lives of patients	1 - no impact	2	3	4	5 - significant impact	Average
Ability to work	20% 3	6.67% 1	20% 3	26.67% 4	26.67% 4	3.33 15
Ability to travel	33.33% 5	26.67% 4	6.67% 1	26.67% 4	6.67% 1	2.47 15
Ability to exercise	6.67% 1	33.33% 5	26.67% 4	20% 3	13.33% 2	3.00 15
Ability to perform household chores	13.33% 2	42.86% 6	20% 3	13.33% 2	13.33% 2	2.73 15
Ability to care for children	42.86% 6	26.67% 4	6.67% 1	6.67% 1	15.38% 2	2.21 14
Ability to fulfill family obligations	20% 3	33.33% 5	26.67% 4	13.33% 2	6.67% 1	2.53 15
Ability to spend time with family and friends	26.67% 4	42.86% 6	13.33% 2	13.33% 2	6.67% 1	2.33 15

Both Rethink and CBCN reported from the 2012 survey that the social impact of this disease spreads across all aspects of a patient's life, restricting an individual's employment and career, ability to care for children and dependents, and their ability to be social and meaningfully participate in their community. When respondents were asked in the 2012 survey what other kinds of impacts living with metastatic breast cancer has had on their quality of life, the following responses were noted:

- Among those who were employed, 71% of patients identified significant restrictions to their ability to work;
- Among those with children or dependents, 21% identified significant restrictions and 53% some or moderate restrictions to their caregiving responsibilities;
- 49% of patients identified significant restrictions and 38% identified some or moderate restrictions to their ability to exercise;
- 42% of patients identified significant restrictions and 42% identified some or moderate restrictions to their ability to pursue hobbies and personal interests;
- 41% of patients identified significant restrictions and 41% identified some or moderate restrictions to their ability to participate in social events and activities;
- 31% of patients identified significant restrictions and 46% identified some or moderate restrictions to their ability to volunteer;
- 25% of patients identified significant restrictions and 43% identified some or moderate restrictions to their ability to self-manage other chronic diseases or health issues;
- 22% of patients identified significant restrictions and 52% identified some or moderate restrictions to their ability to spend time with loved ones.

Both Rethink and CBCN also reported from the 2012 survey on the financial burden associated with living with breast cancer and how it extends far beyond any loss of income during a temporary or permanent absence from employment. CBCN and Rethink stated that in addition to the loss of income during illness, breast cancer patients can also incur substantial costs associated with treatment and disease management. In the 2017 survey, CBCN reported that 86% of HR-positive metastatic patients indicated the cost of prescription medications had a significant or some impact on their treatment decision-making and quality of life.

The following responses taken from the 2012 survey further illustrate the financial burden associated with living with breast cancer:

- Nearly one third of patients indicated that the cost of medication, the cost of alternative treatments (i.e. massage, physiotherapy, etc.) to manage symptoms and side effects, and the time required to travel to treatment had a significant or debilitating impact on their quality of life.
- 24% of patients indicated that the costs associated with travel had a significant or debilitating impact on their quality of life, and 41% of patients indicated that it had some or moderate impact on their quality of life.

CBCN found that in addition to the loss of income during illness, metastatic breast cancer patients can incur substantial costs associated with treatment and disease management. Through research on the financial impact of breast cancer on patients, CBCN identified the following:

- 80% of breast cancer patients report a financial impact due to their illness.
- 44% of patients have used their savings, and 27% have taken on debt to cover costs.

Both CBCN and Rethink also reported from the 2012 survey that other experiences identified by patients with breast cancer included: guilt, the feeling of being a burden on caregivers, fear of death, poor body image, not knowing what functionality will be lost, fear of impact of the cancer and the loss of a parent on children, not knowing what will happen to children, the loss of support of loved ones, martial stress/loss of fidelity and affection from husband.

3.1.2 Patients' Experiences with Current Therapy for HR-positive HER2-negative Advanced or Metastatic Breast Cancer

Both CBCN and Rethink reported that the goals of current treatment options for metastatic breast cancer include controlling the progression of the disease (extending life), and reducing cancer-related symptoms (extending or stabilising quality of life). They also submitted that treatment options and effectiveness may vary among type of cancer, location of cancer, and how symptoms are experienced. They note that for HR-positive patients in particular, treatment options are typically limited to hormonal therapies and chemotherapy.
Reports from the CBCN 2017 survey found that of the 65 patients who indicated they are living with HR-positive breast cancer, the majority of respondents experienced metastases to their bones, liver and lungs, and two patients experienced metastases to their brain as well. Most of the patients (56 patients) had been treated with surgery, 48 patients had undergone radiation therapy, 48 patients had received hormone therapy, and 51 patients had been treated with chemotherapy previously.

According to the 2017 survey, the key factors influencing respondent's decision-making around treatments were indicated as follows:

1. Effectiveness of the treatment - how well the treatment stabilized their disease and delayed progression of their disease.

2. Prolonging life without sacrificing quality of life - being able to maintain productive, active lives with minimal disruption to daily routines.

3. Side effect management - minimizing risk while stabilizing their disease.

4. Cost and accessibility of treatments - affordability and ease of accessing treatments.

In the CBCN 2017 survey, respondents were asked how important progression-free survival was in considering treatments; the HR- positive metastatic patients revealed that efficacy of the treatment is critical to their decision-making. While a majority (98%) of respondents indicated that progression-free survival of six months or more would influence their treatment decisions, 83% responded that progression-free survival of three to five months was very important to them, and 69% indicated that even a progression-free survival of less than three months would be very important to them.

The following are patient responses elaborating on the importance of effectiveness in their decision-making:

- *"The most important factors for me are progression free survival and quality of life"*
- *"Anything to prolong my survival and maintain quality of life"*
- *"Survival is of upmost importance to me"*

CBCN found that respondents cited quality of life as a key factor in treatment-making decisions. In the 2017 survey, 100% of the respondents reported that quality of life was very or somewhat important to them when considering treatment options:

- *"Quality of life is more important to me than quantity. I want what time I have left to be somewhat of a life. I don't want to spend the whole time being so sick that I am incapacitated"*
- *"I want to live as long as possible with a good quality of life. "*

According to the 2012 survey, when asked what level of side effects and how much impact on one's quality of life would be worth extending progression-free disease by six months, respondents indicated that this assessment could only be determined by an individual patient, in this circumstance.

The following were some of the responses noted when respondents of the 2012 survey were asked to rate how much impact different symptoms of cancer and cancer treatment would be considered tolerable:

- Approximately two-thirds of respondents indicated that when it comes to fatigue, nausea, depression, problems with concentration, memory loss, diarrhea and insomnia, some or a moderate impact on one's quality of life would be considered acceptable, and approximately one quarter of respondents indicated that a strong or debilitating impact would be considered acceptable. CBCN found this response was verified by the 2017 survey results, with the majority of respondents indicating that these symptoms were considered acceptable to them.
- 70% of respondents indicated that when it comes to pain, some or a moderate impact on one's quality of life would be considered acceptable, and 27% of respondents indicated that a strong or debilitating impact would be considered acceptable. CBCN found that these results were also corroborated by the 2017 survey, as the majority of respondents indicated that they were willing to somewhat accept pain as a side effect of their treatment.

The following were the responses noted when respondents of the 2012 survey were asked about their willingness to tolerate risk with a new treatment:

- 34% were willing to accept serious risk with treatment if it would control the disease.
- 45% were willing to accept some risk with treatment.
- 21% were very concerned and felt less comfortable with serious risks with treatment.

According to the responses from key informant interviews conducted by CBCN, it was submitted that women with HR- positive breast cancer should have access to and the option of taking the drugs that are available. CBCN stated that most patients are well aware of the adverse effects of treatment up front and they want to make a personal choice that works for them.

The following responses from respondents help illustrate the need for personal choice:

- *"I think patients (ESPECIALLY young patients) should be given more decision making power in terms of access to radical treatments to control disease. […] With two small children, I am determined to access any treatment that can extend my life and I hate struggling with doctors for this access."*
- *"I believe that I would prefer to tolerate severe restrictions in the quality of my life, if it meant that I would be able to have a longer period without progression."*
- *"Had you asked me some of these questions four years ago, the answers would have been different. My oncologist tells me that I am running out of treatment options. […] It is very scary to face the day (soon) when I will have no treatment and the cancer will be allowed to run its course."*

CBCN and Rethink also reported from the 2012 survey on patients' access to local resources and support during treatment. It was reported that many patients living with cancer experience significant barriers and challenges around availability of health care services and quality childcare in their community.

The following were the responses noted from the 2012 survey questions about the availability of supports such as childcare, transportation, and alternative treatments in patients' communities.

- Among patients with children or other dependents, 53% indicated that there is minimal or no access to appropriate care for their loved ones when they are experiencing debilitating symptoms related to their cancer, and 40% identified barriers to accessing quality care during cancer treatment.

Other barriers that were mentioned in the 2012 survey included: not qualifying for insurance at work, inability to change employers due to loss of insurance, and the prohibitive cost of new treatment options.

One respondent stated: "*Many of the next step treatments are very expensive (and not covered by government programs) and it is a HUGE struggle to get (coverage). (…) When dealing with an incurable disease the last thing you want to have to do is spend time on a letter writing campaign to argue about whether or not you should receive the drugs [recommended by your physician].At about $1500.00 a week, I don't know many who can afford that."*

Rethink reported responses from 15 respondents who provided information about the different treatments they had undergone since their diagnosis. Of these respondents, six reported that they had disease progression with the treatment.

Treatments Received	n	Treatments Received	n
Letrozole	12	Goserelin	3
Paclitaxel	7	Denosumab	3
Exemestane	6	Everolimus	3
Tamoxifen	6	Doxorubicin	2
Palbociclib	5	Leuprorelin	1
Capecitabine	4	Protein-bound paclitaxel	1
Docetaxel	4	Zoledronate	1
Anastrozole	4	Cyclophosphamide	1
Fulvestrant	4	Filgrastim	1

Rethink reported that joint pain was the most commonly reported side effect from the treatments listed above (73% of the 15 respondents), followed by nausea (67%), muscle pain (60%), back pain (60%), and insomnia (60%).

Patients reported that they faced financial challenges as a result of their cancer treatment, 67% faced financial challenges due to lost income from work absences, 47% as a result of drug costs, 40% due to parking costs, and 27% due to accommodation costs. Rethink indicated that this is noteworthy due to the reduced travel requirements for treatment with ribociclib.

Below were patients' comments on the benefits of a cancer drug that can be taken orally:

- "*With the Ribociclib, I take two pills in the morning and that's it.*"
- *"I know I still go to the doctor, but now, it's like once a month."*
- *"Until you are a cancer patient or a chronic illness patient and you have to go to the doctor and hospital all the time, that's when you really appreciate being able to just take a pill and know that it's helping fight without you actually having to go to the hospital or put your life on hold."*

3.1.3 Impact of Advanced or Metastatic Breast Cancer and Current Therapy on Caregivers

Caregiver experience was not provided by CBCN and Rethink. Rethink posted an online caregiver survey. However, there were no respondents.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations with Ribociclib

According to the 2012 survey, both CBCN and Rethink reported on the impact and value to patients with the new treatment under review. In particular, it was very important for patients to have quality of life when receiving treatment for metastatic disease. Respondents reported the importance to have the energy to attend children's activities and to spend time with family and friends.

CBCN reported that patients have an expectation that ribociclib will extend progression-free survival and allow them to live a better quality of life than if they were to receive chemotherapy or other hormonal therapies with more significant toxicity profiles. CBCN believes that these values align with the results of the phase III Monaleesa-2 trial.

CBCN reported that the phase III trial Monaleesa-2 trial concluded that ribociclib was generally well tolerated by patients. CBCN noted that the most common side effects reported by patients in the clinical trial were neutropenia, nausea, fatigue, diarrhea, alopecia and vomiting. All patients that CBCN interviewed shared that their side effects were minimal to

non-existent and that their quality of life, including productivity and ability to regain mobility and perform daily functioning, had improved on ribociclib.

When asked about the impact of treatment options to patients, CBCN reported that respondents stressed the importance of having diverse treatment options available to them, particularly so that they could avoid having to turn to chemotherapy as a treatment option. CBCN argues that by delaying the progression of the disease, this treatment can relieve cancer-related symptoms, and improve a patient's quality of life. When living with no or with minimal cancer-related symptoms, and with minimal side effects from the treatment, patients are able to reduce the impact of cancer on their ability to care for children and dependents, continue with their employment and earn income, spend time with loved ones and participate in their life in a meaningful way by engaging in social activities, travelling, maintaining friendships, and pursuing personal interests.

Rethink asked patients to evaluate the important outcomes for their breast cancer treatment on a scale of 1 (not important) to 5 (very important). From the results, listed in the table below, all of the listed outcomes were considered important with an average score over 4.5. Outcomes such as controlling disease and ensuring longer survival were rated more important than reducing symptoms and managing side effects. Rethink suggests that patients and patient values prioritize long-term health outcomes over short-term relief.

Impact of outcome for breast cancer treatment	1 - not important	2	3	4	5 - very important	Average
Controlling disease	0.00% 0	0.00% 0	0.00% 0	0.00% 0	100% 15	5.00 15
Reducing symptoms	0.00% 0	0.00% 0	6.67% 1	0.00% 0	93.33% 14	4.87 15
Maintaining quality of life	0.00% 0	0.00% 0	6.67% 1	13.33% 2	80% 12	4.73 15
Managing side effects	0.00% 0	0.00% 0	6.67% 1	6.67% 1	86.67% 13	4.80 15
Achieving NED (no evidence of disease)	0.00% 0	6.67% 1	0.00% 0	20% 3	73.33% 11	4.60 15
Ensuring longer survival	0.00% 0	0.00% 0	0.00% 0	0.00% 0	100% 15	5.00 15

Rethink also asked respondents if they would be willing to tolerate new side effects from new drugs to ensure progression-free survival for a period of time. On a scale of 1 (will not tolerate side effects) to 10 (will tolerate significant side effects) respondents gave an average score of 7, again suggesting that patient values prioritize health outcomes. Rethink provided further support of this with a patient's comment: "*I would put up with a lot to save my own life*".

CBCN stated that the value of extending the time that their cancer is progression-free to patients cannot be overestimated. CBCN indicates that patients living with metastatic breast cancer are aware that their advanced disease will progress with worsening symptoms until death, and that they would embrace opportunities to try new treatments, even if benefits may be as little as a six-month extension of progression-free disease.

3.2.2 Patient Experiences with Ribociclib

CBCN was able to find two Canadian patients with experience with ribociclib. The first patient had been on treatment since July 2017 (3 months on ribociclib). The first respondent is female and is accessing ribociclib for her metastatic breast cancer through a clinical trial in Ontario. Ribociclib is the first treatment she has been prescribed. The second respondent has been on treatment since May 2017 (5 months on ribociclib). She is accessing treatment through a clinical trial in Quebec and has had previous treatment with surgery, radiation, and Zoladex/ Goserelin.

Rethink had seven respondents who reported receiving ribociclib, all of whom were post-menopausal women with HR-positive, HER2-negative advanced breast cancer. Of these respondents, Rethink found that five respondents received ribociclib in combination with Femara (letrozole), six respondents had received other treatments prior to ribociclib, and two respondents reported progression-free survival on ribociclib. Of these respondents, 4 were treated for three months or less, two were treated for three to six months, and one was treated for more than one year.

Respondents responding to the Rethink survey were asked to rate the change to their quality of life on ribociclib compared to other therapies they had received on a scale of 1 (much worse) to 5 (much better). Rethink found the average scores for every category to be 3 or higher.

The responses noted in the table below suggest that respondents consider ribociclib as moderately effective for controlling disease progression and changes for metastatic cancer symptoms.

Change to quality of life on ribociclib	1 – much worse	2	3	4	5 – much better	Average
Metastatic cancer symptoms	0.00% 0	16.67% 1	33.33% 2	16.67% 1	33.33% 2	3.67 6
Drug side effects	0.00% 0	28.57% 2	42.86% 3	14.29% 1	14.29% 1	3.14 7
Controlling disease progression	14.29% 1	0.00% 0	42.86% 3	0.00% 0	42.86% 3	3.57 7
NED (no evidence of disease)	33.33% 2	0.00% 0	33.33% 2	0.00% 0	33.33% 2	3.00 6

Below were comments made by respondents interviewed by Rethink to help illustrate their experiences with ribociclib:

- *"I felt better almost immediately."*
- *"This drug, so far for me, is working and it's not making me feel sick; it's allowing me to live my life as I normally would."*
- *"As a result of this cycle of the medication, I've stopped needing to have my lungs drained"*
- *"I considered myself very lucky to be on this drug."*

Rethink survey respondents also reported on the effect of taking ribociclib had on their day-to-day lives:

- *"I was getting to a point where I spent all my time in bed. Now, I can get out and I can walk short distances and I can work on my computer and I can have lunch with friends."*
- *"I go to the gym four times a week; I work everyday; I go see my family; I do everything; life is normal."*
- *"I'm not feeling as fragile."*

Rethink found that respondents did not report any practical difficulties accessing ribociclib or its associated blood test but did report issues pertaining to accessing the clinical trials.

Respondents interviewed by CBCN also reported on the impact of the treatment on the disease. Both respondents expressed personal satisfaction with the treatment and noted that their oncologists are pleased with ribociclib controlling and stabilizing their disease.

- "*I noticed the impact immediately. My lymph nodes were very painful and pronounced early in my diagnosis and within a month of this treatment, they started going down in size. It used to be very debilitating, and I couldn't even lie on my side. I just had my 3 month scan and it confirmed what I suspected-my nodes have reduced in size and there has not been any further progression of my disease!"-Patient 1*
- *"My last scan was just two weeks ago and I'm happy to say that everything is stable right now. My oncologist (and I) are both really happy with that this treatment seems to be working for me!"-Patient 2*

In addition, both respondents reported on assessing the risks associated with the treatment. Respondents were well aware of the possible risks of ribociclib and were made aware that all patients can respond differently to side effects. Both respondents interviewed found the side effects to be minimal. CBCN states that Patient 1 expressed that she had experienced mild nausea and fatigue in the first month, and occasional indigestion but that she considered all of her symptoms to be minor and tolerable. Patient 2 shared that she had experienced thinning hair and a lowered white blood cell count, but stated that neither of these conditions were intolerable to her.

- *"If this is cancer treatment, bring it on! This is nothing compared to what other chemo agents do to patients!"* Patient 1
- *"There are no side effects with this treatment that are not acceptable to me. I had fears about my white blood cells being lowered, but so far I would say the impact has been very minimal. "*-Patient 2

When asked about alternatives, both respondents noted that chemotherapy would have likely been an alternative option for them, and both expressed strong desires to avoid the side effects and intolerability of extensive chemotherapy regimens. CBCN reports that Patient 1 mentioned that without this treatment, she would have likely been immediately started on chemotherapy and potentially radiation, while Patient 2 maintained that she would have explored experimental therapies as she did not want to do chemotherapy.

- *"I would have tried to look at new experimental treatments, as I did not want chemo. But when I got my diagnosis, I wanted ribociclib- I knew about the results –it would be devastating if I had not been able to access it"*-Patient 2

In commenting on the social and financial impact of the treatment, respondents interviewed by CBCN did not discuss the financial impact of the treatment, but did discuss the impact that access to ribociclib had on their quality of life and ability to be productive. CBCN notes that Patient 1 stated that at the point of diagnosis she was no longer able to be active. She would previously go for 75 kilometer bike rides, but just prior to her treatment she was unable to exercise. Following her treatment, CBCN reports she is once again able to be active and has resumed cycling again.

- *"I am grateful for being able to resume my life without missing a beat." "I feel so blessed to be able to access this treatment. The fact that if I lived somewhere else I would not have access to this treatment is heartbreaking". -Patient 1*
- *"I have so much hope accessing a new medicine-I feel like I'm doing something to be able to heal." I wish all women could get access to it. It made me forget about cancer for a while. I don't have to be at the hospital so much and I don't have to give up my life, I can just live with cancer" - Patient 2*

3.3 Additional Information

No additional information was provided by CBCN or Rethink Breast Cancer.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from the all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact implementation of ribociclib in combination with letrozole:

Clinical factors:

- Generalizability of data to use ribociclib in combination with other aromatase inhibitors
- Monthly monitoring and bloodwork for neutropenia, which is not required with letrozole monotherapy

Economic factors:

- Large number of patients eligible for treatment
- Cost effectiveness of add-on treatment of a new, high cost, drug

Please see below for more details.

4.1 Factors Related to Comparators

Various aromatase inhibitors are available for initial treatment of advanced or metastatic disease in estrogen-receptor positive, HER2 negative breast cancer. These include anastrozole, exemestane and letrozole. PAG noted that the MONALEESA-2 trial compared ribociclib plus letrozole to letrozole alone. PAG is seeking information with other aromatase inhibitors.

PAG noted that palbociclib, another drug in the same class, recently completed review at pCODR for the same patient population. PAG is seeking information comparing ribociclib to palbociclib: is one better than the other and under what circumstances would ribociclib be preferred to palbociclib or vice-versa?

4.2 Factors Related to Patient Population

PAG noted that this is a large patient population.

If recommended for funding, PAG is seeking guidance on the appropriateness of:

- adding ribociclib for patients who are already on letrozole but not yet progressed
- use with other aromatase inhibitors
- switching patients who are already on other aromatase inhibitors but not yet progressed to ribociclib plus letrozole
- switching palbociclib and ribociclib, if patient is intolerant to one
- continuing treatment if there is oligoprogression

PAG noted the pERC recommendation for palbociclib identified that patients should not be resistant to prior (neo)adjuvant aromatase inhibitor therapy, not have active or uncontrolled metastases to the central nervous system. Would the same apply to the ribociclib, if recommended funding? In addition, PAG noted the MONALEESA-2 trial excluded patients with previous neoadjuvant or adjuvant therapy with a nonsteroidal aromatase inhibitor, unless the disease-free interval was more than 12 months. This is similar to the PALOMA-2 trial for palbociclib where prior adjuvant or neoadjuvant treatment with a nonsteroidal aromatase inhibitor was allowed unless disease had recurred while the patient was receiving the therapy or within 12 months after completing therapy.

In addition, PAG is seeking information on post-progression therapies and the impact of those therapies on cost-effectiveness, particularly on the use of everolimus and exemestane after ribociclib compared to use of chemotherapy after ribociclib.

PAG recognizes that there may not be data on the use of ribociclib plus letrozole in patients who have been previously treated for metastatic disease with other aromatase inhibitors but indicated there may be pressure from oncologists and patients to use ribociclib plus letrozole as second-line, which is out of scope of this current review.

4.3 Factors Related to Dosing

Ribociclib is taken daily for 21 days followed by 7 days off while letrozole is taken daily continuously. PAG has concerns that the dosing of ribociclib being different than letrozole may cause confusion for some patients and there is a risk of dosing error.
PAG noted that one tablet strength is available and dose adjustments are made by adjusting the number of tablets. There would be no drug wastage when dose adjustments are made. However, there are concerns with pill burden as the recommended dose would be three tablets.

In addition, PAG is seeking information on the dose intensity and treatment duration used in the trial compared to what the dose intensity and treatment duration would be expected in clinical practice and the impact on the ICER.

4.4 Factors Related to Implementation Costs

PAG noted that additional health care resources may be required to monitor and treat toxicities and monitor drug-drug interactions. Specifically, PAG noted that patients on aromatase inhibitors are not seen by oncologists on a monthly basis. However, due to the high incidence of neutropenia and risk for QT interval prolongation and hepatobiliary toxicities with the addition of ribociclib, patients will need to be seen monthly for monitoring and bloodwork. Additional monitoring for drugs that may increase QT prolongation while patients are taking ribociclib would be necessary.

As ribociclib is added on to existing therapy, there will be a large budget impact given the large number of patients with estrogen-receptor positive, HER-2 negative breast cancer and the high cost of the combination compared to letrozole alone and other aromatase inhibitors.

4.5 Factors Related to Health System

As ribociclib is administered orally, chemotherapy units and chair time would not be required. As an oral drug, ribociclib can be delivered to patients more easily than

intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.6 Factors Related to Manufacturer

None identified.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One clinician input was provided for ribociclib for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as an initial endocrine-based therapy. Input was provided as a joint submission from three medical oncologists. Their input is summarized below.

The medical oncologists providing input noted that ribociclib plus letrozole compared to letrozole alone improved progression-free survival. However, it was noted that there are added toxicities of ribociclib not seen with letrozole alone. Clinicians noted that the eligible patient population, key benefits and harms, and sequencing of ribociclib would be similar to the pCODR review of palbociclib for HR-positive HER2-negative advanced or metastatic breast cancer. However, there is no direct evidence of ribociclib versus palbociclib.

Please see below for details from the clinician input.

5.1 Current Treatment(s) for HR-positive HER2-negative Advanced or Metastatic Breast Cancer

Endocrine therapy alone or plus palbociclib (for those with private coverage or on clinical trials) were identified as current treatments for advanced or metastatic breast cancer. Bone agents were considered as part of supportive care.

5.2 Eligible Patient Population

The clinicians providing input indicated that there would be high incidence and/or prevalent patient population, similar to the population considered by the pCODR review of palbociclib in combination with letrozole, for the treatment of postmenopausal women with HR-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

Post-menopausal women treated with an aromatase inhibitor as a first agent would be eligible for palliative endocrine therapy, some patients may also receive tamoxifen. Pre-menopausal women with ovarian suppression (GnRH analogue) would also be eligible for ribociclib.

5.3 Identify Key Benefits and Harms with Ribociclib

Clinician input reported the benefits and harms of ribociclib were the same as palbociclib. There were some harms such as an increased risk of neutropenia and diarrhea. Clinicians also noted that there were more frequent monitoring and visits.

5.4 Advantages of Ribociclib Over Current Treatments

Clinicians noted that there is no direct evidence of ribociclib versus palbociclib as initial endocrine therapy for HR-positive HER2-negative advanced or metastatic breast cancer. Clinician input indicated that ribociclib compared to letrozole alone had improved progression-free survival but at a worse toxicity profile. Although ribociclib was more toxic than letrozole alone and associated with asymptomatic neutropenia and elevated AST levels, ribociclib was considered to be overall well tolerated. Improving progression-free survival was considered important as it delays time until patients require subsequent treatment with chemotherapy.

Clinician input also reported not many issues after ribociclib use and monitoring is also required if patients are on endocrine therapy alone.

With respect to any unmet needs that ribociclib would fulfil, clinicians providing input indicated that metastatic breast cancer is still treated with palliative intent and there is still a need for better treatments.

5.5 Sequencing and Priority of Treatments with Ribociclib

Clinician input reported that ribociclib would be sequenced the same as palbociclib. Ribociclib could be used instead of palbociclib or as an alternative treatment, adding more choices for patients and clinicians. It was also identified that sequencing with everolimus is unknown.

5.6 Companion Diagnostic Testing

None.

5.7 Additional Information

None.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of ribociclib in combination with standard endocrine therapy compared to standard endocrine therapy alone as first-line treatment in post-menopausal women with hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer (ABC).

Supplemental Questions relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Critical appraisal of the Manufacturer's submitted network meta-analysis (NMA) comparing endocrine-based therapies as first-line treatment in post-menopausal women with HR-positive and HER2-negative ABC.
- Critical appraisal of the Manufacturer's submitted indirect treatment comparison (ITC) and matching-adjusted indirect treatment comparison (MAIC) of ribociclib-letrozole and palbociclib-letrozole as first-line treatment in post-menopausal women with HR-positive and HER2-negative ABC.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 3. Outcomes considered most relevant to patients, based on input from patient advocacy groups, are indicated in bold.

Table 3: Selection criteria.

Trial Design	Patient population	Intervention	Appropriate comparators*	Outcomes
Published or unpublished RCTs	• Post-menopausal women (≥18 years) with HR-positive and HER2-negative ABC not amenable to surgery (locally recurrent or metastatic disease) • Treatment naïve (no previous treatment for ABC)	Ribociclib plus endocrine therapy Endocrine therapy can include: • Aromatase inhibitors (e.g., letrozole, anastrozole, exemestane) • Estrogen receptor downregulators (e.g., fulvestrant) • Selective estrogen receptor modulators (e.g., tamoxifen)	• Endocrine therapy alone • Palbociclib plus letrozole	• **PFS** • OS • ORR • DOR • CBR** • PRO and **QOL** • Safety
Abbreviations: **ABC** – advanced/metastatic breast cancer; **CBR** – clinical benefit rate; **DOR** – duration of response; **HR** – hormone receptor; **HER2** - human epidermal growth factor receptor 2; **ORR** – objective response rate; **OS** – overall survival; **PFS** – progression-free survival; **PRO** – patient-reported outcomes; **QOL** – quality of life; **RCTs** – randomized controlled trials.				

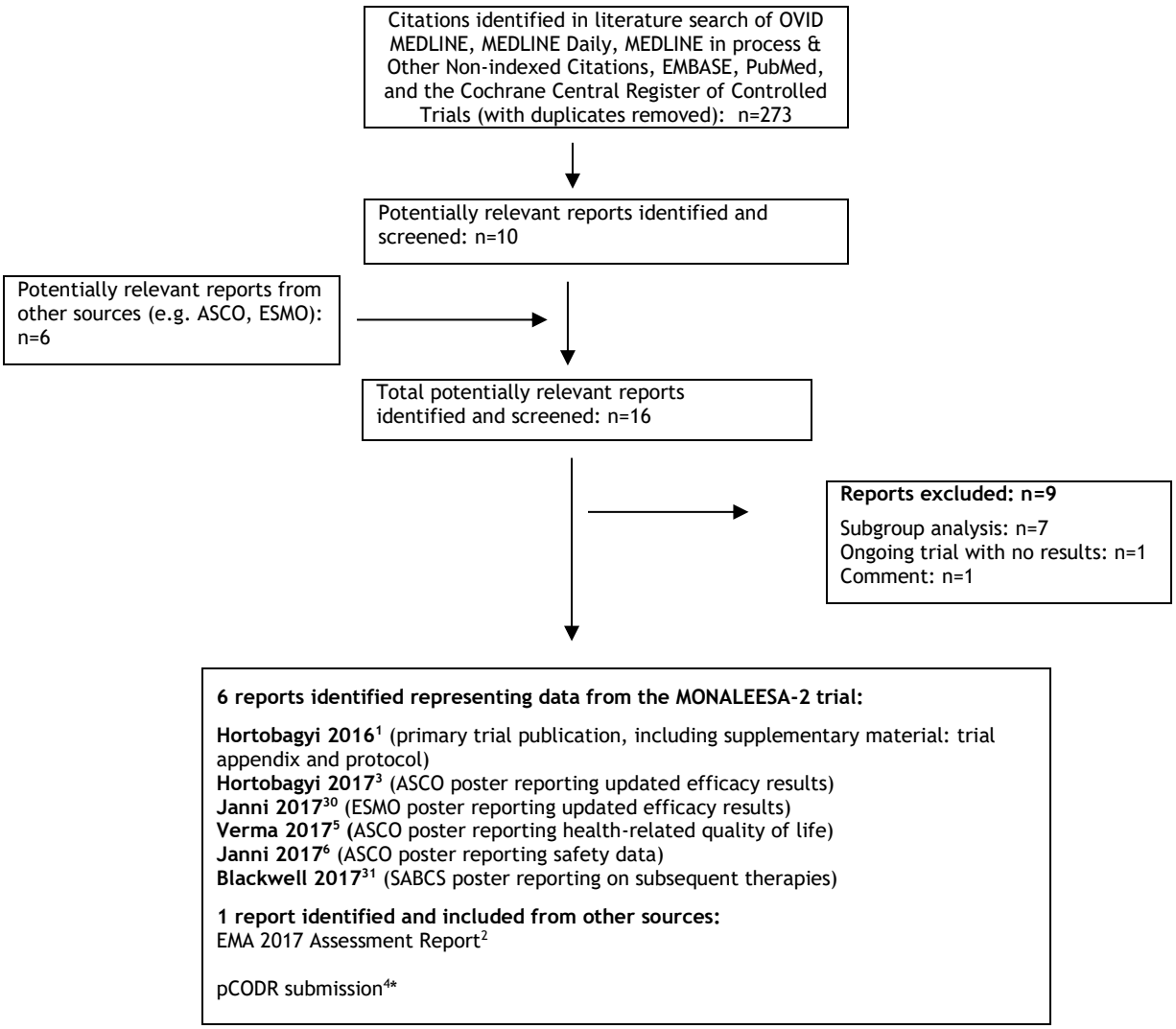
**Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*
***Defined as the sum of complete and partial response and stable disease for 24 weeks or more.*

6.3 Results

6.3.1 Literature Search Results

Of the 16 potentially relevant reports identified, seven reports[1-3,5,6,30,31] were included in the pCODR systematic review and nine reports[17,32-39] were excluded. Studies were excluded because they reported subgroup analysis data not of interest to this review,[32-38] reported an ongoing trial with no results,[17] or were commentary in nature.[39]

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of Studies



**Note: Additional data related to MONALEESA-2 were also obtained through requests to the Submitter by pCODR.*

6.3.2 Summary of Included Studies

One randomized controlled trial, MONALEESA-2,[1] was identified that met the eligibility criteria of this review. Characteristics of the trial are summarized in Table 4 and specific aspects of trial quality are summarized in Table 5.

6.3.2.1 Detailed Trial Characteristics

Table 4: Key characteristics of the MONALEESA-2 trial.[1]

Trial design	Eligibility criteria	Intervention	Comparator	Outcomes
MONALEESA-2 Phase 3, double-blind RCT (1:1)[18] Patient enrolment: January 24, 2014-March 24, 2015 Primary data cut-off date: January 29, 2016 Updated data cut-off date: January 2, 2017[3] N randomized=668 N treated=664 Multicentre: 223 sites in 29 countries including Canada[2] Randomization stratified by: • Presence or absence of liver or lung metastases Funded by Novartis Pharmaceuticals	<u>Key inclusion criteria:</u> • Post-menopausal[a] women with HR-positive, HER2-negative advanced (recurrent or metastatic) breast cancer not amenable to curative therapy • Measurable disease[b] or at least one predominantly lytic bone lesion • ECOG 0 to 1 • Adequate bone marrow and organ function <u>Key exclusion criteria:</u> • Previous treatment for advanced disease • Prior (neo)adjuvant treatment with any nonsteroidal aromatase inhibitor unless disease-free interval > 12 months • Previous treatment with any CDK inhibitor • Patients with: o Inflammatory breast cancer o CNS metastases o History of cardiac disease or dysfunction o Impaired gastrointestinal function that altered drug absorption	Ribociclib (oral 600 mg once daily for 3 weeks, one week off in 28-day cycle) + Letrozole (oral 2.5 mg once daily)	Placebo (oral once daily for 3 weeks, one week off in 28-day cycle) + Letrozole (oral 2.5 mg once daily)	<u>Primary</u>: • PFS (investigator assessed)[b] <u>Key Secondary</u>: • OS • ORR (CR or PR)[b] • CBR (sum of CR and PR and stable disease ≥ 24 weeks) • QOL (EORTC QLQ-C30 and QLQ-BR23) • Safety <u>Exploratory:</u> • DOR[b]
		Treatment until disease progression, unacceptable toxicity, death or discontinuation for any other reason.		

Abbreviations: CBR - clinical benefit rate; **CDK -** cyclin-dependent kinase; **CNS** – central nervous system; **CR** – complete response; **DOR -** duration of response; **ECOG** – Eastern Cooperative Oncology Group; **EORTC QLQ -** European Organization for Research and Treatment of Cancer's Core Quality of Life Questionnaire (**C30)** and Breast Cancer Specific Questionnaire **(BR23)**; **HR** –hormone receptor; **HER2**- human epidermal growth factor receptor 2; **ORR** – overall response rate; **OS** – overall survival; **PFS** – progression-free survival; **PR** – partial response; **RCT** – randomized control trial; **RECIST** – Response Evaluation Criteria in Solid Tumors.

[a] – Includes women with prior bilateral oophorectomy, age ≥60, or age < 60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression) and FSH and estradiol in the postmenopausal range per local normal range.[18]
[b] - Assessed according to RECIST version 1.1.

Table 5: Select quality characteristics of included MONALEESA-2 trial.[1,18]

Trial	Treatment vs. comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics approval
MONALEESA-2[1]	Ribociclib + letrozole vs. placebo + letrozole	Investigator assessed PFS	302 PFS events[c] required to provide 93.5% power to detect HR=0.67[a] at a one-sided alpha=0.025 (stratified logrank) using a two-look Haybittle-Peto efficacy stopping boundary.[b]	668	Stratified;[d] central, using interactive response technology (1:1)[18]	Yes[18]	DB[e]	Yes	No	No	Yes

Abbreviations: DB – double-blind; **HR** – hazard ratio; **PFS** - progression-free survival.

Notes:

[a] – Corresponds to an increase in median PFS from 9 months (placebo plus letrozole) to 13.4 months (ribociclib plus letrozole).[18]

[b] – A pre-specified interim analysis occurred when 211 PFS events (70%) were reported. Superiority of ribociclib-letrozole versus placebo-letrozole was concluded if the analysis obtained an HR ≤0.57 with $p<1.29 \times 10^{-5}$.

[c] – Estimated sample size was 650 patients, which was based on a recruitment period of 16 months at a rate of 37 patients per month and assuming a 10% loss of patients to follow-up.[18]

[d] - Randomization was stratified by the presence or absence of liver or lung metastases.

[e] – Patients and investigators were blinded to treatment assignment. Independent blinded data analysists performed the interim analysis of PFS. The final analysis of PFS (and analyses of OS) were performed unblinded, by the trial Sponsor; however, patients and investigators remained blinded to treatment assignment.[18]

a) Trial

MONALEESA-2 is an ongoing, international, multi-centred, phase 3, double-blind, placebo-controlled randomized trial evaluating the efficacy and safety of ribociclib in combination with letrozole as first-line treatment for women with HR-positive, HER2-negative ABC.[1] There were 223 sites in 29 countries, including Canada (8 sites), that participated in the trial.[2] The trial Sponsor, Novartis Pharmaceuticals, oversaw trial conduct including data collection and data analysis, and were involved in manuscript preparation.

Eligibility Criteria

Women enrolled in MONALEESA-2 met the following key criteria:

- post-menopausal (defined by prior oophorectomy, age ≥60, or age <60 and amenorrhea for 12 or more months[i] and follicle stimulating hormone and estradiol in the post-menopausal range per local normal range),[18] HR-positive, and HER2-negative ABC;
- no previous systemic therapy for ABC, including endocrine therapy, chemotherapy and CDK4/6 inhibitors;
- measurable disease by RECIST version 1.1 or at least one predominately lytic bone lesion; and
- an ECOG performance status of 0 or 1.

For a more detailed list of the key eligibility criteria used in the trial refer to Table 4.

Outcomes

The primary outcome of the trial was progression-free survival by local investigator assessment (PFS by INV), according to RECIST. Secondary outcomes included overall survival (OS), overall response rate (ORR), clinical benefit rate (CBR), health-related quality of life (QOL), and safety. Duration of response (DOR) was an exploratory endpoint. Disease status was assessed using computed tomography or magnetic resonance imaging and performed at trial screening, every eight weeks during the first 18 months of the trial, and every 12 weeks thereafter until disease progression or discontinuation of treatment for other reasons. For patients who discontinued for other reasons, disease assessment continued on the same schedule until disease progression or death.[18] An independent review committee, blinded to treatment assignment, prospectively reviewed all imaging data (BICR) at fixed time points (every 8 weeks).

Randomization, Sample Size, and Statistical Analyses

Information on randomization, required sample size, statistical assumptions, and other indicators of trial quality are detailed in Table 5.

Patients were randomized in a 1:1 ratio to the ribociclib-letrozole and placebo-letrozole treatment groups using a centralized[18] and stratified randomization method. Patients were stratified according to the presence or absence of liver and lung metastases.

There were two notable amendments to the trial protocol, which included:

[i] In the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression.

- An increase in the required sample size, from 500 to 650 patients, in order to better characterize the effect of ribociclib and letrozole on OS (amendment 2).[18]
- Earlier conduct of the planned interim analysis of the primary outcome after observing 70% of PFS events (versus the planned 80%) in response to the trial reaching full patient enrollment earlier than expected (amendment 3). This change was not considered to compromise the statistical analysis plan (SAP) of the trial as the interim analysis was performed after all patients had been randomized and was based on a mature dataset (at an almost 80% information fraction) that still allowed for a robust assessment of efficacy and safety.[18]

The SAP specified two efficacy analyses of the primary outcome, which included the interim analysis (noted above) and the final analysis. A two-look Haybittle-Peto stopping boundary was applied to control the type 1 error rate associated with both analyses. The pre-specified criteria for declaring superior efficacy in the ribociclib-letrozole group (over placebo-letrozole) at interim analysis was a hazard ratio (HR) of ≤0.57 and a corresponding p-value of 1.29×10^{-5}.[18] The objective of the final analysis, to be performed when 100% of PFS events have been observed, is to compare PFS by INV between the two treatment groups using a stratified log-rank test at an overall one-sided significance level of 0.025. An improvement in median PFS by INV of at least 4.43 months (assumes median PFS of 13.43 months and 9 months in the ribociclib-letrozole and placebo-letrozole groups, respectively; HR=0.67) is expected in order to demonstrate the superiority of ribociclib-letrozole (Table 5). An analysis of the BICR collected PFS data was also planned and considered a supportive analysis.

For the analysis of OS, the key secondary outcome of the trial, a hierarchical testing procedure was followed such that if the primary outcome was met (that is, superiority of ribociclib-letrozole was demonstrated and statistically significant), OS would be compared between the treatment groups.[18] Specifically, up to four analyses of OS data could be performed; the first two analyses were planned to occur at the time of the interim and final analyses of PFS, and the third and fourth analyses were planned after 300 and 400 deaths, respectively.[18] A Lan-DeMets (O'Brian-Fleming) stopping boundary was applied to control for the type 1 error associated with repeated testing of OS, which set the threshold for statistical significance at $p=3.15 \times 10^{-5}$.[4]

All efficacy analyses, including all secondary outcomes, were performed in the intent-to-treat (ITT) population according to treatment and stratification assignment at randomization. All HRs and 95% confidence intervals (CIs) were estimated using a stratified Cox proportional hazard regression model. Multiple subgroup analyses were planned a priori to explore the internal consistency of the treatment effect based on baseline characteristics, however, they were considered exploratory in nature[18] and therefore uncontrolled for type 1 error arising from multiple comparisons.

Patient–reported health-related QOL was assessed using the EORTC Quality of Life Questionnaire (QLQ)-C30 and the breast-specific module (EORTC QLQ-BR23).[18] The QLQ-C30 measures overall QOL and different aspects of patient functioning. It comprises five function scales (physical, emotional, cognitive, social and role), three symptom scales (fatigue, pain, and nausea and vomiting), a global health and QOL scale, and six single-item scales. The global health status/QOL scale was considered the primary patient-reported variable of interest of the trial, while

specific function scales (physical, emotional, and social) and the breast cancer symptoms scale of the QLQ-BR23 were considered secondary variables of interest. For both instruments, a mean change from baseline of 10% or greater is considered the minimal clinically important difference (MCID). For the scales of interest, mean changes from baseline were compared between treatment groups at selected time points using a linear mixed model that included treatment, stratification factor and baseline score. Differences in least square means between treatment groups were calculated with their corresponding 95% CIs. Time-to-10% deterioration, defined as a worsening in score by at least 10% compared to baseline (with no later improvement above this threshold), was also assessed and evaluated as a time-to-event outcome using Kaplan Meier methods. The treatment groups were compared with a stratified log-rank test and a stratified Cox regression model was used to generate HRs and 95% CIs. Questionnaires were completed every eight weeks after randomization during the first 18 months of the trial, then every 12 weeks until disease progression, death, loss to follow-up or withdrawal of consent, and at treatment discontinuation.

The MONALEESA-2 trial is ongoing, and to date, data from the following efficacy analyses have been published:

- The planned interim analysis of PFS; and first interim analysis of OS with a data cut-off date of January 29, 2016 (trial publication).[1]
- A second interim analysis of OS; and an updated exploratory efficacy analysis of PFS with a data cut-off date of January 2, 2017 (conference poster).[3] In proceeding sections this analysis is referred to as the second updated analysis.
- The analysis of patient-reported QOL with a cut-off date of January 4, 2017 (conference poster).[5]

The safety analysis, which included assessments up to 30 days after treatment discontinuation, was performed in all patients who received at least one dose of study drug and had at least one safety assessment after baseline. The primary safety analysis was performed at the first interim analysis,[1] and a second, updated exploratory analysis of safety was performed on January 4, 2017.[4]

b) Populations

Patient randomization occurred between January 24, 2014 and March 24, 2015. During that period a total of 668 patients were randomized; 334 were allocated to ribociclib-letrozole and 334 were allocated to placebo-letrozole. Overall, the baseline characteristics of patients were well balanced between the two treatment groups (Table 6). Most randomized patients were treated at trial sites in Europe (44.3%) and North America (34.3%), with fewer patients treated in Asia (10.2%).[2] The median age was 62 years, with 44.2% of patients aged 65 and older.[2] All patients had and ECOG performance status of 0 or 1, HR-positive disease, and all but two patients (one in each treatment group) were HER2-negative (99.7%). The majority of patients were white (82.2%), had stage IV disease (99.4%), and a disease-free interval of ≥24 months (59.4%). Approximately one third (34%) of patients had de novo ABC. The most common sites of metastases were bone (any: 73.4%; only: 22%) and visceral (58.8%; lung and/or liver only: 55.8%), and approximately one third (34%) of patients had three or more metastatic sites. The percentages of patients previously treated in the neoadjuvant or adjuvant setting

with endocrine therapy and chemotherapy were 51.8% and 43.6%, respectively. All patients had prior surgery (including biopsy) and approximately half of patients (51.6%) had received prior radiotherapy.[2]

c) Interventions

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

The median time on treatment was comparable between the treatment groups; 13 months in the ribociclib-letrozole group and 12.4 months in the placebo-letrozole group. The median dose intensity was 100% for letrozole in both groups, and 100% and 87.5% for placebo and ribociclib, respectively. Dose reductions and interruptions[ii] were more frequent in patients treated with ribociclib-letrozole compared to placebo-letrozole, and were primary attributable to AEs. In the ribociclib-letrozole treatment group, dose interruptions were required in 76.9% of patients for ribociclib and in 39.5% of patients for letrozole. In the placebo-letrozole group, placebo and letrozole were interrupted in 40.6% and 32.4% of patients, respectively. Dose reductions occurred in 53.9% of patients in the ribociclib-treated group and 7.0% of patients in the placebo-treated group; these were attributed to AEs in 50.6% and 4.2% of patients, respectively.

The use of concomitant medications were permitted in the trial to treat AEs, and manage cancer symptoms and concurrent diseases, and supportive care agents were also allowed. Strong inhibitors or inducers of CYP3A4/5, substrates of CYP3A4/5 with a narrow therapeutic index, medications with a known risk of QT prolongation, other investigative antineoplastic agents, and herbal medicines were not permitted on study.[18] The trial publication did not report data on the actual concomitant medications taken by patients during the trial.

[ii] Assessed in the safety population (n=664).

Table 6: Baseline characteristics of patients included in the MONALEESA-2 trial.[1]

Baseline Characteristics*, n (%) unless otherwise specified	MONALEESA-2	
Treatment Groups	**Ribociclib + letrozole**	**Placebo + letrozole**
No. patients randomized	**334**	**334**
Median age, years (range)	62 (23-91)	63 (29-88)
Race[a]		
White	269 (80.5)	280 (83.8)
Asian	28 (8.4)	23 (6.9)
Black	10 (3.0)	7 (2.1)
Other or unknown	27 (8.1)	24 (7.2)
ECOG performance status:		
0	205 (61.4)	202 (60.5)
1	129 (38.6)	132(39.5)
Disease stage:		
III	1 (0.3)	3 (0.9)
IV	333 (99.7)	331 (99.1)
Hormone-receptor status:		
Estrogen-receptor positive	332 (99.4)	333 (99.7)
Progesterone-receptor positive	271 (81.1)	278 (83.2)
Disease-free interval:		
Newly diagnosed (de novo disease)	114 (34.1)	113 (33.8)
Existing disease		
≤12 months	178 (40)	93 (42)
>12 months to ≤24 months	99 (22)	48 (22)
>24 months	167 (38)	81 (37)
Unknown	0	1 (0.3)
Previous systemic treatment:[b]		
(Neo)adjuvant chemotherapy	146 (43.7))	145 (43.4)
(Neo)adjuvant endocrine therapy	175 (52.4)	171 (51.2)
Anastrozole	47 (14.1)	42 (12.6)
Exemestane	19 (5.7)	25 (7.5)
Goserelin	6 (1.8)	3 (0.9)
Letrozole	34 (10.2)	25 (7.5)
Tamoxifen	140 (41.9)	145 (43.4)
Other	2 (0.6)	4 (1.2)
Number of metastatic sites:		
0	2 (0.6)	1 (0.3)
1	100 (29.9)	117 (35)
2	118 (35.3)	103 (30.8)
≥3	114 (34.1)	113 (33.8)
Site of metastases:		
Breast	8 (2.4)	11 (3.3)
Bone, any	246 (73.7)	244 (73.1)
Bone, only	69 (20.7)	78 (23.4)
Visceral[c]	197 (59.0)	196 (58.7)
Lymph nodes	133 (39.8)	123 (36.8)
Other	35 (10.5)	22 (6.6)
Abbreviations: ECOG – Eastern Cooperative Oncology Group.		
Notes: *There were no significant differences between treatment groups.		

[a] – Race was self-reported.
[b] – Some patients received both chemotherapy and endocrine therapy as neo(adjuvant) treatment.
[c] - Visceral involvement includes liver, lung, and other visceral metastases.

From: The New England Journal of Medicine, Gabriel N. Hortobagyi, Salomon M. Stemmer, Howard A. Burris, et al, Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer, 375, 1738-48. Copyright © (2016) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

d) Patient Disposition

The disposition of patients through the MONALEESA-2 trial is summarized in Table 7, broken down by the first interim analysis[4] and the second updated analysis.[3] There were four patients in the trial, all in the placebo-letrozole group, who did not receive any study medication due to physician or patient decision. The percentages of patients who had discontinued treatment at the time of the first and second updated analyses, respectively, were 41.6% and 60.8% in the ribociclib-letrozole group, and 53.9% and 73.7% in the placebo-letrozole group. Progressive disease (PD) was the primary reason for treatment discontinuation in both groups; however, discontinuations due to PD were higher in the placebo-letrozole group at both time points (ribociclib-letrozole: 26% and 39.8% vs. placebo-letrozole: 43.7% and 60.8%). Conversely, treatment discontinuations attributable to AEs were higher in patients treated with ribociclib-letrozole at both time points (ribociclib-letrozole: 7.5% and 8.1% vs. placebo-letrozole: 2.1% and 2.4%).

Information on the protocol deviations that took place during the trial was not reported in the trial publication, but has been published elsewhere,[2] and reported for the data-cut-off date at first interim analysis. Overall, at least one protocol deviation occurred in 42.4% of patients and major protocol deviations occurred in 6.6% of patients. The major deviations were primarily attributable to selection criteria not being met (Table 7). The low frequency of these deviations, and the generally even distribution of them between the treatment groups, makes it unlikely they influenced the efficacy findings of the trial.

The subsequent anti-cancer therapies received by patients after discontinuation of study treatment are summarized in Table 8.[31] The reported percentages are based on the number of patients in the ribociclib-letrozole (n=203) and placebo-letrozole (n=246) groups that discontinued study treatment at the data cut-off date for the second updated analysis (January 2, 2017). The percentages of patients who received one or more anti-cancer therapies post-study treatment were similar in the two treatment groups (85% in the ribociclib-letrozole group; and 86% in the placebo-letrozole group), with single-agent hormonal therapy being the most common subsequent treatment in both groups (44% and 35%, respectively). The most frequently used hormonal monotherapies (ribociclib-letrozole vs. placebo-letrozole) were fulvestrant (45% vs. 62%), letrozole (36% vs. 21%), and tamoxifen (9% vs. 12%). Median time-to-first subsequent treatment was 24.2 months (95% CI, 20.9-27.6) in the ribociclib-letrozole group and 16.7 months (95% CI, 14.8-19.3) in the placebo-letrozole group.

Table 7: Patient disposition in the MONALEESA-2 trial.[3,4]

Patient Disposition, n (%)	MONALEESA-2			
Treatment groups	**Ribociclib + letrozole**		**Placebo + letrozole**	
Analysis	**1st interim analysis[4,a]**	**2nd updated analysis[3,b]**	**1st interim analysis[4,a]**	**2nd updated analysis[3,b]**
Patients screened	**958**		**-**	
Patients randomized	**334**		**334**	
Received allocated treatment	334 (100)		330 (98.8)	
Did not receive allocated treatment	0		4[c]	
Patients continuing randomized treatment	195 (58.4)	131 (39.2)	154 (46.1)	88 (26.3)
Patients discontinuing randomized treatment	139 (41.6)	203 (60.8)	180 (53.9)	246 (73.7)
Primary reasons for discontinuation:				
Progressive disease	87 (26.0)	133 (39.8)	146 (43.7)	203 (60.8)
Adverse event	25 (7.5)	27 (8.1)	7 (2.1)	8 (2.4)
Patient decision	12 (3.6)	29 (6.0)	13 (3.9)	17 (5.1)
Physician decision	10 (3.0)	16 (4.8)	13 (3.9)	16 (4.8)
Protocol violation	3 (<1)	3 (<1)	1 (<1)	1 (<1)
Death	2 (<1)	4 (1.2)	0	1 (<1)
Lost to follow-up	0	NR	0	NR
Major Protocol deviations:[2]				
Patients with at least one protocol deviation	24 (7.2)	NR	20 (6.0)	NR
Selection criteria not met	24 (7.2)	NR	20 (6.0)	NR
Criteria for prior therapy for ABC not met[d]	15 (4.5)	NR	9 (2.7)	NR
Post-menopausal status not met	2 (<1)	NR	6 (1.8)	NR
Criteria for measurable disease or lytic bone lesion not met	6 (1.8)	NR	3 (<1)	NR
Breast cancer type (HER2 status) not met	1 (<1)	NR	1 (<1)	NR
Concurrent malignancy or malignancy in last three years of randomization	0	NR	1 (<1)	NR
Criteria for advanced disease not met	1 (<1)	NR	0	NR

Abbreviations: **ABC** – advanced breast cancer; **NR** – not reported.

Notes:
[a] – Data cut-off date January 29, 2016.
[b] – Data cut-off date January 2, 2017.
[c] - Four patients did not receive allocated treatment: three due to physician's decision and one due to patient decision.
[d] – Includes patients who took letrozole/anastrozole for more than 14 days or patients who were on any prior (neo) adjuvant anti-cancer therapy that were not stopped at least five half-lives or seven days before randomization.

Table 8: Subsequent anti-cancer therapy received by patients in the MONALEESA-2 trial.[31]

Subsequent anti-cancer therapy, n (%)	Ribociclib + letrozole (n=203)[a]	Placebo + letrozole (n=246)[a]
Received ≥1 subsequent therapy	**172 (85)**	**212 (86)**
Any hormonal therapy alone	**90 (44)**	**87 (35)**
Fulvestrant	40 (45)	53 (62)
Letrozole	32 (36)	18 (21)
Tamoxifen	8 (9)	10 (12)
Any hormonal therapy + targeted therapy/other[b]	**37 (18)**	**58 (24)**
Exemestane	21 (57)	22 (38)
Everolimus	22 (59)	20 (34)
Palbociclib	9 (24)	24 (41)
Any chemotherapy alone	**32 (16)**	**55 (22)**
Capecitabine	18 (56)	21 (38)
Paclitaxel	6 (19)	14 (25)
cyclophosphamide	4 (13)	7 (13)
Any chemotherapy + other[c]	**NR (3)**	**NR (3)**
Any targeted therapy alone	**NR (3)**	**NR (1)**
Other	**0**	NR (1)

Abbreviations: NR – not reported.

Notes:
[a] –Percentage of patients is based on patients who had discontinued study treatment at the January 2, 2017 data cut-off (denominator).
[b] – Includes patients who received hormonal therapy plus targeted therapy plus other therapy.
[c] – Includes patients who received chemotherapy plus hormonal therapy.

e) Limitations/Sources of Bias

Critical appraisal of the MONALEESA-2 trial was based on the primary trial publication, updated data published in posters presented at international symposia, and unpublished data provided to pCODR by the Manufacturer. Overall, the trial was well-conducted. The randomization procedure, method of allocation concealment, and double-blind design were carried out appropriately. The treatment groups were well balanced for important baseline prognostic and patient characteristics, and length of time on treatment was also similar between the groups. There was transparent reporting of the disposition of patients through the trial, and outcome analyses were performed according to the ITT principle.

The trial met its primary endpoint at interim analysis (median follow-up of 15 months) and showed a significant PFS benefit with ribociclib-letrozole compared to placebo-letrozole. The superiority of ribociclib-letrozole demonstrated at interim analysis was based on crossing a stringent threshold of statistical significance. The interim results are likely robust considering the number of PFS events informing the analysis (80%); as much lower event rates are typically associated with overestimating treatment effects.[8] It is possible, however, that the higher incidence of neutropenia in the ribociclib-letrozole treatment group may have introduced bias into the investigator assessment of PFS (in favour of ribociclib-letrozole). The effect of this bias on the results obtained is likely minimal though since the BICR assessment reported PFS findings of similar magnitude.

The SAP of the trial specified the number of efficacy analyses to be performed of the primary outcome and the key secondary outcome, and used statistical tests to control for the probability of type 1 error that arises from multiple comparisons or

"looks" at the trial data. The purpose of these statistical tests is to preserve the overall significance level across the number of planned, specified analyses and the overall power of the trial.[9] In the MONALEESA-2 trial, however, there were at least three analyses performed of the PFS data while the SAP only specified two analyses; analyses were performed on January 29, 2016,[1] June 22, 2016,[4] and January 2, 2017.[3] This is a limitation of the trial, since it is unknown what informed the decision to look at the data at additional time points. Undertaking unplanned interim analyses increases the risk of type 1 error, and consequently, can lead to exaggeration of treatment effects.[9] Therefore, the magnitude of the treatment estimates obtained should be interpreted with some level of caution.

Although the subgroup analyses performed in the trial were pre-specified, and demonstrated a consistent treatment benefit in most of the subgroups examined, caution is warranted in interpreting these results. By testing enough subgroups, false positives results can arise by chance. A proper subgroup analysis includes a statistical test for interaction to assess whether the treatment effect differs among subgroups, opposed to individual tests within each subgroup.[9] Since the trial protocol indicated no adjustments were made for multiple testing and no tests for interaction were performed,[18] the subgroup analysis results should be considered exploratory and interpreted within this context.

The assessment of patient-reported health-related QOL is limited,[5] and therefore as currently presented, may not fully capture the QOL experience of all patients in the trial. At many assessment time points patient compliance in completing questionnaires was low (missing data), which can bias findings since there likely are systematic differences in the characteristics of patients who complete and don't complete questionnaires. Further, the QOL results were only available in poster form, and therefore have not been fully peer-reviewed, as these sources selectively reported QOL outcomes.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

The efficacy outcomes in the MONALEESA-2 trial are summarized in Table 9.

The median duration of patient follow-up was 15.3 months at the first interim analysis,[1] and 26.4 months at the second updated analysis.[3]

Progression-free survival by Investigator Assessment

Progression-free survival was defined as the time from randomization to the date of first documented progression or death due to any cause.[18]

The interim analysis took place when 243 PFS events were observed.[1] Due to a delay in reporting from trial sites, the number of PFS events contributing to the interim analysis was actually greater than the planned 70% of events specified in the SAP.[18] The trial met its primary outcome (crossed the pre-specified Haybittle-Peto boundary for superiority) and demonstrated a statistically significant improvement in PFS by INV in the ribociclib-letrozole treatment group. Median PFS by INV was not reached in the ribociclib treatment group (95% CI, 19.3-not reached) and was 14.7 months (95% CI, 13.0-16.5) in the placebo group (HR=0.56, 95% CI, 0.43-0.72; p=3.29 x 10^{-6}; Figure 2).

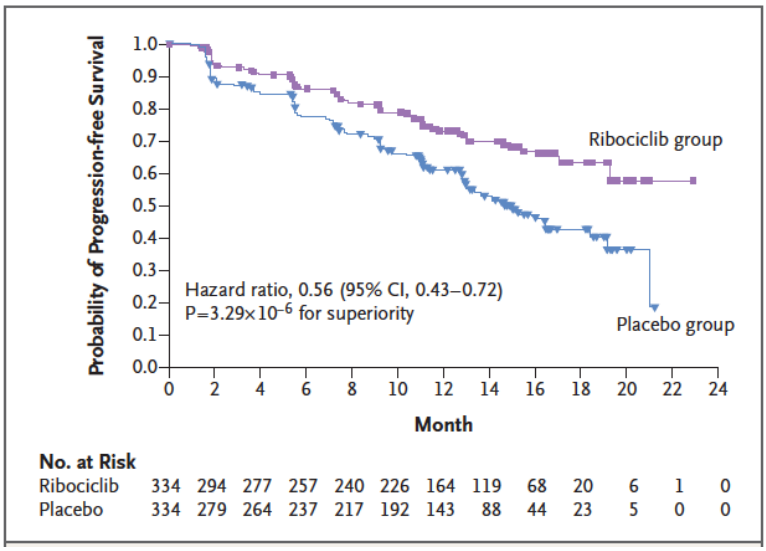
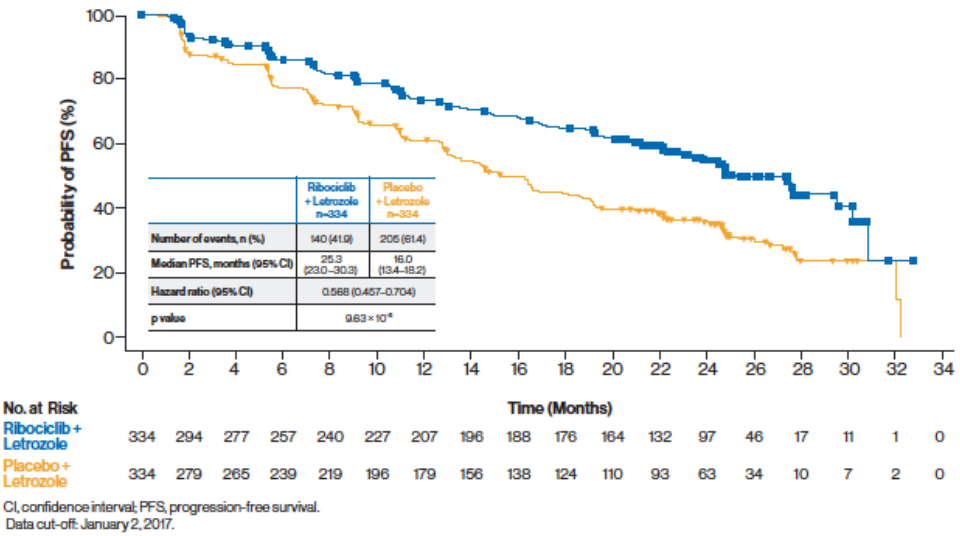


Figure 2: Progression-free survival by investigator assessment in the MONALEESA-2 trial at interim analysis (data cut-off-date January 29, 2016).[1]

From: The New England Journal of Medicine, Gabriel N. Hortobagyi, Salomon M. Stemmer, Howard A. Burris, et al, Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer, 375, 1738-48. Copyright © (2016) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

The second updated analysis of PFS by INV,[3] which was based on 345 PFS events, showed a sustained PFS benefit with ribociclib-letrozole after an additional 11 months of follow-up (Figure 3); median PFS by INV was 25.3 months (95% CI, 23.0-30.3) in the ribociclib-letrozole group and 16 months (95% CI, 13.4-18.2) in the

placebo-letrozole group, which is a 9.3-month improvement in PFS with ribociclib-letrozole (HR=0.57, 95% CI, 0.46-0.70; p=9.63 x 10^{-8}).



CI, confidence interval; PFS, progression-free survival.
Data cut-off: January 2, 2017.

Figure 3: Progression-free survival by investigator assessment in the MONALEESA-2 trial at the second updated analysis (data cut-off-date January 2, 2017).[3]

Source: full-text conference poster provided by Novartis Pharmaceuticals Canada.

The results of BICR analyses supported the investigator assessment at both analyses (interim analysis: PFS BICR HR=0.59, 95% CI, 0.41-0.85, p=0.002; updated analysis BICR: HR=0.56, 95% CI, 0.42-0.77, p=1.07 x 10^{-4}).[1,3] Of note, there was a sizeable difference between the number of PFS events determined by investigator and by BICR. For both analyses the number of BICR assessed PFS events were approximately half of the number of investigator assessed PFS events (refer to Table 8), both overall and by treatment group. The concordance rate between PFS by INV and BICR at first interim analysis was 80.5% in the ribociclib-letrozole group and 69.5% in the placebo-letrozole group.[2] Investigator assessments of progressive disease were not confirmed by BICR in approximately 60% of cases (60.7% in the ribociclib-letrozole group and 60.0% in the placebo-letrozole group).[2] Investigation into the possible source(s) of the discrepancy between the two assessment methods identified new or worsening bone lesions as a likely contributing factor since PD assessment of these lesions is more subjective than other lesion types.[2] It is unlikely, however, that the discordance between the different assessments biased efficacy results since the proportions of discrepancies were not systematically different between treatment groups at both analysis time points.

The PFS benefit observed at interim analysis with ribociclib-letrozole in all patients was consistent in all pre-specified patient subgroups;[1] however, for patients with bone-only disease (n=147) and patients who had received prior therapy consisting of non-steroidal aromatase inhibitors (n=53), the confidence limits crossed the line of unity, suggesting statistical non-significance. The estimated HRs (vs. placebo-letrozole) for the various subgroups ranged between 0.39 and 0.69 (Figure 4). Similar subgroup results were obtained at the second updated PFS analysis (data not shown).[3]

Table 8: Efficacy outcomes in the MONALEESA-2 trial.[1,3]

Efficacy Outcomes	MONALEESA-2			
Treatment Groups	**Ribociclib + letrozole (n=334)**	**Placebo + letrozole (n=334)**	**Ribociclib + letrozole (n=334)**	**Placebo + letrozole (n=334)**
Analysis	1st Interim analysis[1]		2nd Updated analysis[3]	
Data cut-off date	January 29, 2016		January 2, 2017	
Median follow-up, months	15.3		26.4	
Primary Outcome – Investigator Assessed PFS[a]				
No. PFS events (%)	93 (27.8)[2]	150 (44.9)[2]	140 (41.9)	205 (61.7)
Median PFS, months (95% CI)	Not reached (19.3-not reached)	14.7 (13.0-16.5)	25.3 (23.0-30.3)	16 (13.4-18.2)
HR* (95% CI; one-sided p-value)	0.56 (0.43-0.72; $p=3.29 \times 10^{-6}$)		0.57 (0.46-0.70; $p=9.63 \times 10^{-8}$)	
PFS rate at 12 months (95% CI)	72.8 (67.3-77.6)	60.9 (55.1-66.2)	-	-
PFS rate at 18 months (95% CI)	63.0 (54.6-70.3)	42.2 (34.8-49.5)	-	-
PFS rate at 24 months (95% CI)	-	-	54.7 (48.5-60.5)[4]	35.9 (30.3-41.5)[4]
BICR-assessed PFS				
No. PFS events (%)	50 (15.0)[2]	72 (21.6)[2]	NR	NR
Median PFS, months (95% CI)	22.9 (NE, NE)[2]	NE (NE, NE)[2]	NR	NR
HR* (95% CI; one-sided p-value)	0.59 (0.41-0.85; p=0.002)		0.56 (0.42-0.77; p=0.0001)	
Key Secondary Outcomes				
ORR[b] in all patients (ITT), n	136	92	142	96
% (95% CI)	40.7 (35.4-46.0)	27.5 (22.8-32.3)	42.5 (37.2-47.8)	28.7 (23.9-33.6)
p-value	p<0.001		p=NR	
CR	9 (2.7)	7 (2.1)	13 (3.9)	8 (2.4)
PR	127 (38.0)	85 (25.4)	129 (38.5)	88 (26.3)
SD	95 (28.4)	111 (33.2)	90 (26.9)	107 (32.0)
PD	19 (5.7)	40 (12.0)	20 (6.0)	40 (12.0)
Unknown	18 (5.4)	16 (4.8)	16 (4.8)	16 (4.8)
CBR[c] in all patients (ITT), n	266	243	268[4]	244[4]
% (95% CI)	79.6 (75.3-84.0)	72.8 (68.0-77.5)	79.9 (75.6-84.2)	73.1 (68.3-77.8)
p-value	p=0.02		p=NR	
No. patients with measurable disease at baseline, n	256	243	257	245
ORR[b] in patients with measurable disease at baseline, n	135	91	NR	NR
% (95% CI)	52.7 (46.6-58.9)	37.1 (31.1-43.2)	54.5 (48.4-60.6)	38.8 (32.7-44.9)

Efficacy Outcomes	MONALEESA-2			
Treatment Groups	**Ribociclib + letrozole (n=334)**	**Placebo + letrozole (n=334)**	**Ribociclib + letrozole (n=334)**	**Placebo + letrozole (n=334)**
p-value	p<0.001		p=NR	
CR	8 (3.1)	6 (2.4)	11 (4.3)	7 (2.9)
PR	127 (49.6)	85 (34.7)	129 (50.2)	88 (35.9)
SD	95 (37.1)	111 (45.3)	90 (35)	107 (43.7)
PD	13 (5.1)	31 (12.7)	14 (5.4)	31 (12.7)
Unknown	13 (5.1)	11 (4.5)	12 (4.7)	11 (4.5)
CBR[c] in patients with measurable disease at baseline, n	205	176	NR	NR
% (95% CI)	80.1 (75.2)	71.8 (66.2-77.5)	80.2 (75.3-85.0)	71.8 (66.2-77.5)
p-value	p=0.02		p=NR	
Overall Survival				
No. deaths, %	23 (6.9)	20 (6.0)	50 (15.0)	66 (19.8)
Median, months (95% CI)	NE	NE	Not reached	33 (33-not reached)
HR* (95% CI; two-sided p-value)	1.13 (0.62-2.06; p=0.653)[2,4]		0.75 (0.52-1.08; p=0.059)	

Abbreviations: **BICR** – blinded independent central review; **CBR** – clinical benefit rate; **CI** – confidence interval; CR – complete response; **HR** = hazard ratio; **ITT** – intent-to-treat; **NE** – not estimable; No./n = number; **NR** – not reported; **ORR** – overall response rate; **PD** – progressive disease; **PFS** – progression-free survival; **PR** – partial response; **SD** – stable disease.

Notes:

* HR < 1 favours ribociclib-letrozole.

[a] Defined as the time from randomization to date of the first documented disease progression or death due to any cause.

[b] Defined as the sum of CR plus PR. There were 66 (19.8%) and 75 (22.5%) patients in the ribociclib plus letrozole group and placebo plus letrozole group, respectively, that had neither a CR nor PD. These patients had no measureable disease at baseline, and best overall response was evaluated according to RECIST version 1.1.

[c] Defined as the sum of CR plus PR and SD for 24 weeks or more.

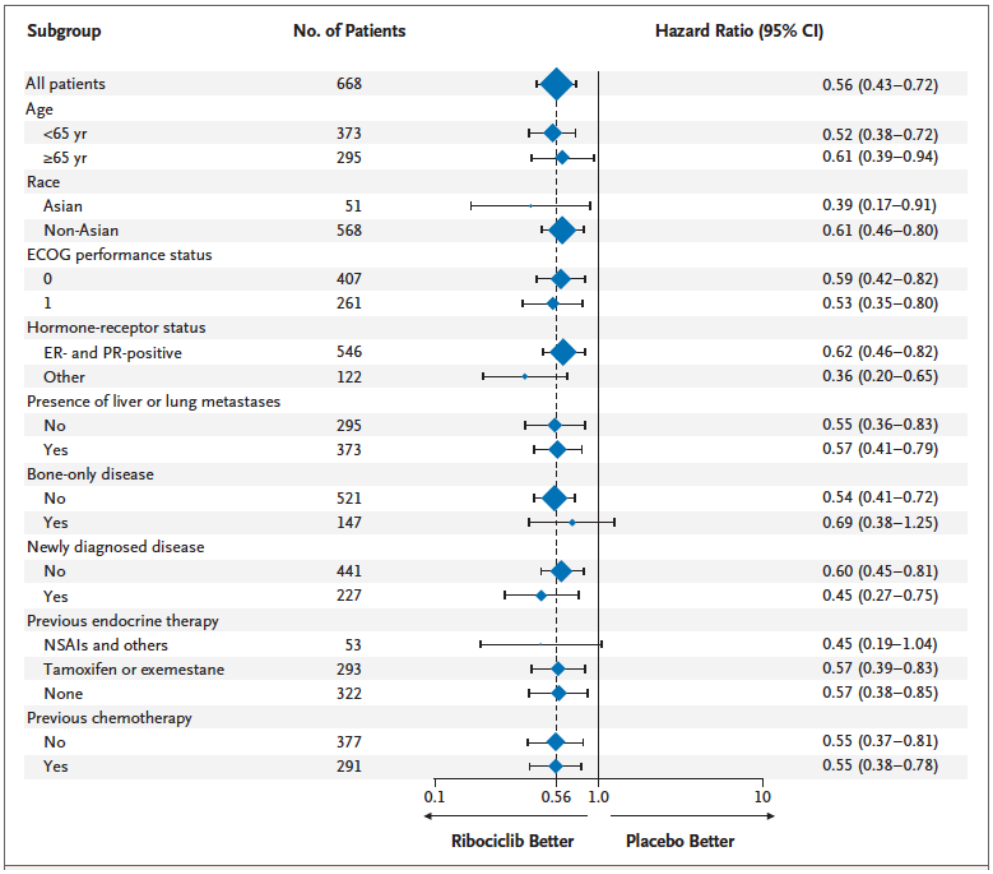


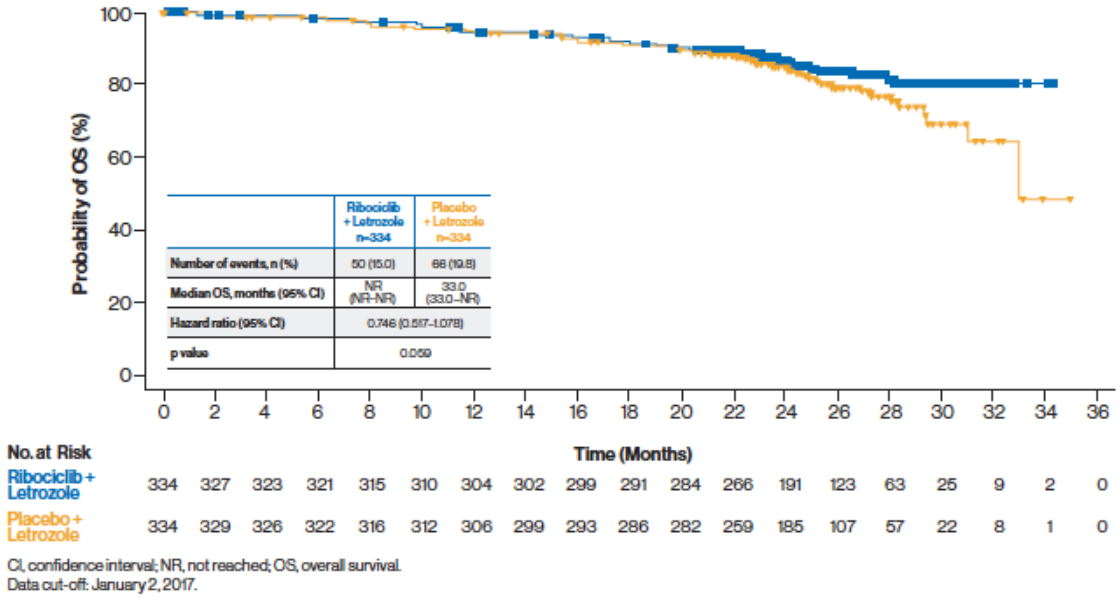
Figure 4: Subgroup analyses of progression-free survival by investigator assessment in the MONALEESA-2 trial at interim analysis (data cut-off-date January 29, 2016).[1]

From: The New England Journal of Medicine, Gabriel N. Hortobagyi, Salomon M. Stemmer, Howard A. Burris, et al, Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer, 375, 1738-48. Copyright © (2016) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Overall Survival

At interim analysis, data on OS were immature with 6.9% of deaths (n=23) observed in the ribociclib-letrozole group and 6% (n=20) observed in the placebo-letrozole group.[1] These results did not meet the pre-specified stopping boundary for statistical significance (median OS was not estimable in either group, HR=1.13, 95% CI, 0.62-2.06; p=0.653).[4]

At the second updated analysis,[3] the OS data remained immature with 15% (n=50) of deaths and 19.8% (n=66) of deaths in the ribociclib-letrozole and placebo-letrozole groups, respectively (Figure 5). Median OS was not reached in the ribociclib-letrozole group and 33 months in the placebo-letrozole group (HR=0.75, 95% CI, 0.52-1.08); this difference in OS between the groups still did not reach the threshold for statistical significance (p=0.059).



CI, confidence interval; NR, not reached; OS, overall survival.
Data cut-off: January 2, 2017.

Figure 5: Overall survival by investigator assessment in the MONALEESA-2 trial at second updated analysis (data cut-off-date January 2, 2017).[3]

Source: full-text conference poster provided by Novartis Pharmaceuticals Canada.

Tumour Response Outcomes (Overall Response, Clinical Benefit Rate, Duration of Response)

Overall, tumour response outcomes were significantly and consistently higher in the ribociclib-letrozole treatment group relative to placebo-letrozole, at both analysis time points (Table 8).[1,3]

At first interim analysis,[1] the ORR in the ribociclib-letrozole treatment group was 40.7% compared to 27.5% in the placebo-letrozole group (absolute difference=13.2%; p<0.001); the corresponding ORRs at the second updated analysis were 42.5% and 28.7% (absolute difference=13.8%; p-value not reported), respectively.

Clinical benefit rate, defined as the sum of complete and partial responses and stable disease for 24 weeks or more, was 79.6% and 72.8% in the ribociclib-letrozole group and placebo-letrozole groups, respectively, at first interim analysis (absolute difference of 6.4%; p=0.02);[1] the corresponding ORRs at the second updated analysis were 79.9% and 73.1% (absolute difference of 6.8%; p-value not reported).[3]

In the subgroup of patients who had measurable disease at baseline, the results for both ORR and CBR were similar to the ITT population (Table 8).[1,3] Data on DOR, an exploratory endpoint of the trial, were reported for this subgroup in patients who had a confirmed complete or partial response.[30] Median DOR was 26.7 (95% CI, 24.0-not reached) months in the ribociclib-letrozole group and 18.6 months (95% CI, 14.8-23.1) in the placebo-letrozole group.

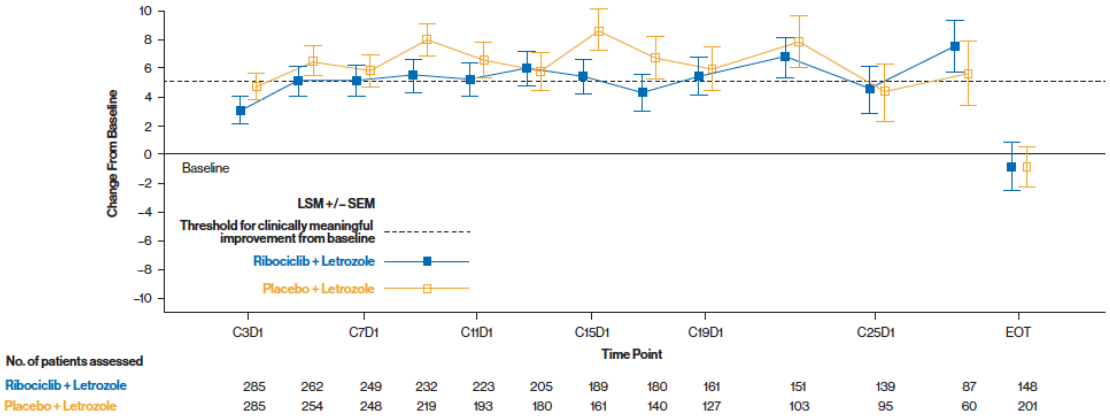
Quality of Life

Published results on the health-related QOL outcomes of the trial have focused primarily on the EORTC QLQ-C30 data, with limited results reported for the QLQ-B23 assessment.[5] Overall, no clinically meaningful differences in health-related QOL were evident between the two treatment groups.

Patient compliance in completing QLQ-C30 questionnaires was reported as high during the treatment phase of the trial, with >90% compliance up to cycle 19; however, sample sizes declined substantially thereafter, as patients did not complete questionnaires after disease progression. Overall, patient compliance for the QLQ-B23 was similar to that observed with the QLQ-C30, however, for two scales compliance seemed particularly poor (upset by hair loss and sexual enjoyment). Baseline scores for all the QLQ scales were similar between the treatment groups.[4]

During the treatment phase of the trial, global health status/QOL scores (the primary variable of interest), were slightly improved (increase in scores) from baseline in both treatment groups, and then declined (worsened) by the end of treatment (Figure 6). Assessment of mean changes from baseline demonstrated no clinically meaningful differences between the treatment groups in the global health status/QOL scores at any time point (that is, no difference met the MCID threshold of ≥10 points).[5] Results of the linear mixed regression model analysis showed no significant effect of treatment, time, or treatment by time interactions on the global health status/QOL score; the estimated mean difference in changes in global health status/QOL scale score between the treatment groups was -1.5 (95% CI, -4.0-1.0).[2] Time-to-deterioration of the global health status/QOL score by at least 10% was also similar between the treatment groups (HR=0.94, 95% CI, 0.72-1.24; Figure 7).[5]

Analyses performed of the secondary variables of interest, which included the three QLQ-C30 functioning scales, the QLQ-B23 breast cancer symptoms scale,[4] and the QLQ-C30 symptom scales (fatigue, nausea and vomiting, and pain), also demonstrated no clinically significant changes from baseline or differences between treatment groups at any time point (the MCID threshold of ≥10 points was not met; data not shown).

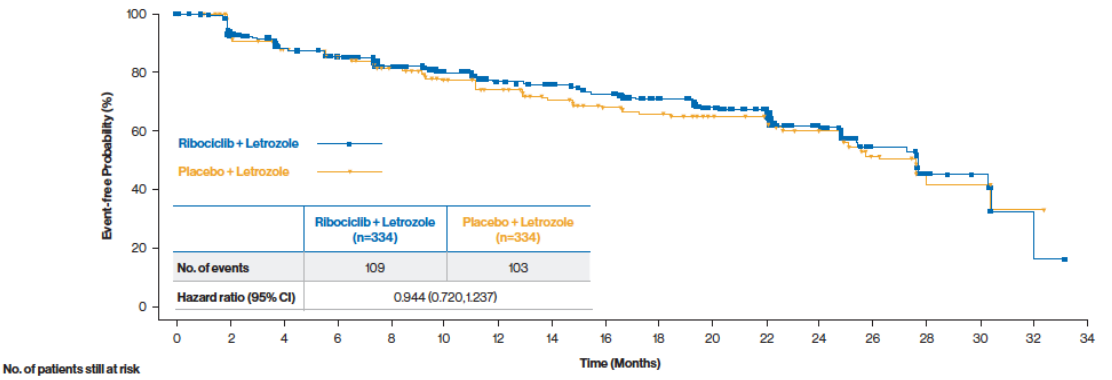


No. of patients assessed													
Ribociclib + Letrozole	285	262	249	232	223	205	189	180	161	151	139	87	148
Placebo + Letrozole	285	254	248	219	193	180	161	140	127	103	95	60	201

C, Cycle; D, Day; EOT, end of treatment; LSM, least squares mean; SEM, standard error of the mean.
Data cut-off: January 4, 2017. The time profile provides the average estimates for the change from baseline for the interval from baseline up to the respective cycle as derived from the linear effects model. Positive changes from baseline are related to improvement in HRQoL.
>5 point improvement from baseline in HRQoL score defined as clinically meaningful.
Only patients with baseline scores and at least one non-missing post-baseline assessment are included for change from baseline analysis which was performed using the linear effect model with treatment, stratification factor, and baseline score in the model.

Figure 6: Changes from baseline in the EORTC QLQ-C30 Global Health Status/QOL Score by treatment group in the MONALEESA-2 trial (data cut-off-date January 4, 2017).[5]

Source: full-text conference poster provided by Novartis Pharmaceuticals Canada.



No. of patients still at risk																
Ribociclib + Letrozole	334	277	250	236	215	196	178	170	159	145	128	119	78	37	13	10	1	0
Placebo + Letrozole	334	262	240	222	200	178	162	138	120	106	92	89	55	25	9	9	1	0

CI, confidence interval.
Data cut-off: January 4, 2017. Full analysis set.

Figure 7: Time-to-definitive deterioration of EORTC QLQ-C30 Global Health Status/QOL Score from baseline in the MONALEESA-2 trial (data cut-off-date January 4, 2017).[5]

Source: full-text conference poster provided by Novartis Pharmaceuticals Canada.

Harms Outcomes

Safety

A summary of the safety outcomes in the MONALEESA-2 trial at first interim analysis,[1,6] and at the second exploratory analysis,[3] are provided in Table 9. The safety analysis population included 334 patients in the ribociclib-letrozole group and 330 patients in the placebo-letrozole group. Results were similar at the first and second analyses with no new safety concerns identified at the last data-cut-off; therefore, the results of the first interim analysis[1] are discussed below.

At first interim analysis, AEs of any grade and causality (in at least 15% of the safety population) occurred in 98.5% of patients treated with ribociclib-letrozole and 99.1% of patients treated with placebo-letrozole. The majority of AEs in both treatment groups were low grade (grade 1 or 2). The AEs (any grade) occurring more frequently in the ribociclib-letrozole treatment group (vs. placebo-letrozole) included neutropenia (74.3% vs. 5.2%), nausea (51.5% vs. 28.5%), diarrhea (35% vs. 22.1%), alopecia (33.2% vs. 15.5%), leucopenia (32.9% vs. 3.9%), vomiting (29.3% vs. 15.5%), anemia (18.6% vs. 4.5%), increased alanine aminotransferase (ALT, 15.6% vs. 3.9%), and increased aspartate aminotransferase (AST, 15% vs. 3.6%). Treatment interruptions, dose reductions, and treatment discontinuations due to AEs were all higher in the ribociclib-letrozole treatment group (vs. placebo-letrozole) and occurred in 68% (vs. 13.3%),[6] 50.6% (vs. 4.2%), and 7.5% (vs. 2.1%) of patients, respectively.

Grade 3 or 4 AEs occurred in substantially more patients treated with ribociclib-letrozole (81.2%) compared to patients treated with placebo-letrozole (32.7%); the majority of higher grade events in the ribociclib group were attributable to neutropenia (59.3%). In this group neutropenia required dose interruptions in 49.7% of patients and dose reductions in 31.1% of patients. It was noted that most dose adjustments occurred early in the treatment phase (during first 6 cycles), and treatments discontinuations due to neutropenia occurred in <1% of patients.[6] Febrile neutropenia was reported in five patients (1.5%) in the ribociclib-letrozole group (vs. no patients in placebo-letrozole group).

The frequency of serious AEs (SAEs)[7] was also higher in the ribociclib-letrozole group (21.3%) compared to placebo-letrozole (11.8%); 7.5% and 1.5% of these events, respectively, were related to study treatment. The most common SAEs (ribociclib-letrozole vs. placebo-letrozole) were abdominal pain (1.5% vs. 0%), vomiting (1.5% vs. 0.6%), constipation (1.2% vs. 0%), nausea (1.2% VS. 0.6%), anemia (1.2% vs. 0.3%), febrile neutropenia (1.2% vs. 0%), dyspnea (1.2% vs. 0.3%), pleural infusion (0.6% vs. 1.2%) and increase in ALT (1.2% vs. 0%).[7]

Deaths

Considering both analyses, there were 10 deaths that occurred during the treatment phase of the trial (≤ 30 days after last dose of study medication); seven (2.1%) in the ribociclib-letrozole treatment group, and three (0.9%) in the placebo-letrozole group. The causes of death in the ribociclib-letrozole group included underlying breast cancer (n=2), acute respiratory failure (n=2), pneumonia (n=1), sudden death (n=1) and death due to unknown cause (n=1).[1,3] The sudden death was attributed to ribociclib and occurred in association with grade 3 hypokalemia and a grade 2 prolongation in the QTcF interval resulting from a prohibited concomitant medication with a known risk for QT prolongation.[1] The causes of death in the placebo-letrozole treatment group included underlying breast cancer (n=2)[1] and a subdural hematoma (n=1).[3]

Table 9: Safety outcomes in the MONALEESA-2 trial.

AE, n (%)	MONOLEESA-2						MONALEESA-2					
	1st Interim analysis[1,a]						Updated safety analysis[3,e]					
	Ribociclib + letrozole n=334			Placebo + letrozole[b] n=330			Ribociclib + letrozole n=334			Placebo + letrozole n=330		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any AE	329 (98.5)	221 (66.2)	50 (15.0)	320 (97.0)	105 (31.8)	3 (0.9)	331 (99.1)	232 (69.5)	56 (16.8)	322 (97.6)	117 (35.5)	6 (1.8)
Neutropenia[c]	248 (74.3)	166 (49.7)	32 (9.6)	17 (5.2)	3 (0.9)	0	214 (64.1)	139 (41.6)	29 (8.7)	16 (4.8)	3 (0.9)	0
Nausea	172 (51.5)	8 (2.4)	0	94 (28.5)	2 (0.6)	0	178 (53.3)	8 (2.4)	0	101 (30.6)	2 (0.6)	0
Infections	168 (50.3)	12 (3.6)	2 (0.6)	140 (42.4)	7 (2.1)	1 (0.3)	187 (56.0)[4]	23 (6.9)[4]	3 (0.9)[4]	162 (49.1)[4]	8 (2.4)[4]	1 (0.3)[4]
Fatigue	122 (36.5)	7 (2.1)	1 (0.3)	99 (30.0)	3 (0.9)	0	138 (41.3)	9 (2.7)	1 (0.3)	107 (32.4)	3 (0.9)	0
Diarrhea	117 (35.0)	4 (1.2)	0	73 (22.1)	3 (0.9)	0	128 (38.3)	8 (2.4)	0	81 (24.5)	3 (0.9)	0
Alopecia	111 (33.2)	NA	NA	51 (15.5)	NA	NA	115 (34.4)	0	0	53 (16.1)	0	0
Leucopenia	110 (32.9)	66 (19.8)	4 (1.2)	13 (3.9)	2 (0.6)	0	52 (15.6)[4]	28 (8.4)[4]	2 (0.6)[4]	9 (2.7)[4]	1 (0.3)[4]	0[4]
Vomiting	98 (29.3)	12 (3.6)	0	51 (15.5)	3 (0.9)	0	112 (33.5)	12 (3.6)	0	55 (16.7)	3 (0.9)	0
Arthalgia	91 (27.2)	2 (0.6)	1 (0.3)	95 (28.8)	3 (0.9)	0	111 (33.2)	2 (0.6)	1 (0.3)	108 (32.7)	4 (1.2)	0
Constipation	83 (24.9)	4 (1.2)	0	63 (19.1)	0	0	93 (27.8)	4 (1.2)	0	71 (21.5)	0	0
Headache	74 (22.2)	1 (0.3)	0	63 (19.1)	1 (0.3)	0	90 (26.9)	1 (0.3)	0	69 (20.9)	2 (0.6)	0
Hot flush	70 (21.0)	1 (0.3)	0	78 (23.6)	0	0	82 (24.6)	1 (0.3)	0	84 (25.5)	0	0
Back pain	66 (19.8)	7 (2.1)	0	58 (17.6)	1 (0.3)	0	81 (24.3)	10 (3.0)	0	67 (20.3)	1 (0.3)	0
Cough	65 (19.5)	0	NA	59 (17.9)	0	NA	77 (23.1)	0	0	70 (21.2)	0	0
Anemia[d]	62 (18.6)	3 (0.9)	1 (0.3)	15 (4.5)	4 (1.2)	0	69 (20.7)	6 (1.8)	2 (0.6)	19 (5.8)	4 (1.2)	0
Decreased appetite	62 (18.6)	5 (1.5)	0	50 (15.2)	1 (0.3)	0	69 (20.7)	5 (1.5)	0	52 (15.8)	1 (0.3)	0
Rash	57 (17.1)	2 (0.6)	0	26 (7.9)	0	0	NR	NR	NR	NR	NR	NR
Increased ALT	52 (15.6)	25 (7.5)	6 (1.8)	13 (3.9)	4 (1.2)	0	NR	NR	NR	NR	NR	NR
Increased AST	50 (15.0)	16 (4.8)	3 (0.9)	12 (3.6)	4 (1.2)	0	NR	NR	NR	NR	NR	NR
Neutrophil count decreased	NR	NR	NR	NR	NR	NR	72 (21.6)	53 (15.9)	3 (0.9)	4 (1.2)	1 (0.3)	0
Any SAE	71 (21.3)			39 (11.8)			85 (25.4)[4]			51 (15.5)[4]		
AEs leading to dose interruption	NR (68)			NR (13.3)			NR			NR		
AEs leading to dose reduction	169 (50.6)			14 (4.2)			NR			NR		
AEs leading to treatment discontinuation	25 (7.5)[6]			7 (2.1)[6]			NR			NR		

Abbreviations: AE(s) – adverse event(s); **n**= number; **ALT** – alanine aminotransferase; **AST** - aspartate aminotransferase; **NA** – not applicable since not included in National Cancer Institute Common Terminology Criteria for AEs, version 4.03; **NR** – not reported; **SAE** – serious adverse event.

Notes:

[a] All-cause AEs reported in at least 15% of patients in the safety population; data cut-off date of January 29, 2016.
[b] Four patients who were randomized to placebo plus letrozole did not receive either placebo or letrozole.
[c] Neutropenia includes a decreased neutrophil count and granulocytopenia.
[d] Includes both anemia and a decreased hemoglobin level.
[e] All-cause AEs reported in at least 20% of patients in the safety population; data cut-off date of January 4, 2017, which provides an additional 11 months of follow-up.

6.4 Ongoing Trials

One ongoing, randomized phase 3 trial, MONALEESA-3,[16,17] was identified as being relevant to this review, and is summarized in Table 10.

Table 10: Ongoing trial evaluating ribociclib combined with endocrine therapy as first-line treatment for HR-positive, HER2-negative ABC.

Trial Design	Eligibility Criteria	Intervention and Comparator	Trial Outcomes
MONALEESA-3 (NCT02422615) Phase 3, multicentre, double blind, placebo-controlled Status: active, not recruiting N=725 randomized 31 countries including Canada Patient Enrolment Dates: June 2015 – not reported Data cut-off: February 19, 2020 Funded by Novartis Pharmaceuticals	Key Inclusion Criteria: • Male or post-menopausal female age ≥ 18 years • Histologically or cytologically confirmed diagnosis of HR-positive, HER2-negative advanced (recurrent or metastatic) breast cancer not amenable to curative therapy • Measurable disease by RECIST version 1.1 or at least one predominantly lytic bone lesion • Measurable disease[b] or at least one predominantly lytic bone lesion • ECOG 0 to 1 • Adequate bone marrow and organ function Key Exclusion Criteria: • Previous treatment for advanced disease (chemotherapy, fulvestrant, any CDK inhibitor) • Patients with: o Inflammatory breast cancer o CNS metastases (unless at least 4 weeks from prior therapy to starting study treatment, and have stable CNS tumour at time of trial screening, and not receiving steroids or enzyme inducing medications for anti-epileptic brain metastases) o History of cardiac disease or dysfunction	Ribociclib (oral 600 mg once daily for 3 weeks, one week off in 28-day cycle) + fulvestrant (500mg intramuscularly every 28 days with additional dose on day 15 of cycle 1) *versus* Placebo (oral 600 mg once daily for 3 weeks, one week off in 28-day cycle) + fulvestrant (500mg intramuscularly every 28 days with additional dose on day 15 of cycle 1)	Primary: • PFS by investigator assessment Secondary: • OS • PFS by BICR • ORR • Time-to-response/DOR • CBR • QOL • Safety
Abbreviations: BICR – blinded independent central review; **CBR –** clinical benefit rate; **CDK –** cyclin-dependent kinase; **CNS** – central nervous system; **DOR –** duration of response; **ECOG –** Eastern Cooperative Oncology Group; **HER2** - human epidermal growth factor receptor 2; **HR** – hormone receptor; **ORR** – objective response rate; **OS** – overall survival; **PFS** – progression-free survival; **QOL –** quality of life; **RECIST** – Response Evaluation Criteria in Solid Tumors.			

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review:

- Critical appraisal of the Manufacturer's submitted network meta-analysis (NMA) comparing endocrine-based therapies as first-line treatment in post-menopausal women with HR-positive and HER2-negative ABC.
- Critical appraisal of the Manufacturer's submitted indirect treatment comparison (ITC) and matching-adjusted indirect treatment comparison (MAIC) of ribociclib-letrozole and palbociclib-letrozole as first-line treatment in post-menopausal women with HR-positive and HER2-negative ABC.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical appraisal of the Manufacturer's submitted network meta-analysis (NMA) comparing endocrine-based therapies as first-line treatment in HR-positive, HER2-negative ABC

7.1.1 Objective

The objective of this section is to summarize and critically appraise the methods and results of the manufacturer's submitted NMA comparing ribociclib-letrozole to other available endocrine-based therapies as first-line treatment in post-menopausal women with HR-positive and HER2-negative ABC (target population), in order to inform the pCODR clinical and economic evaluations of ribociclib-letrozole to relevant comparators. Results of the NMA have been published (conference poster) for the primary outcome of progression-free survival (PFS),[10] and therefore, are the focus of this critical appraisal. The appraisal was also informed by unpublished information provided by the Submitter to pCODR in the form of a NMA full report.[40]

7.1.2 Findings

Rational and Objectives
Multiple therapies are available for the first-line treatment of HR-positive, HER2-negative ABC. The objective of the NMA was to compare ribociclib-letrozole with other available treatments that have not been directly compared in randomized trials in order to derive relative estimates of treatment effect and use them a supportive evidence for the pCODR submission.

Systematic Review
A systematic review was performed to identify evidence on the efficacy of available treatments in the first-line setting. Evidence was identified according to the PICOS (population, intervention, comparators, outcomes, study design) criteria set out in Table 11. The search was focused on randomized controlled trials (RCTs) that evaluated endrocrine therapy (letrozole, anastrozole, exemestane, tamoxifen, fulvestrant), targeted therapy (everolimus, palbociclib, ribociclib, abemaciclib), and chemotherapy (capecitabine, doxorubicin, paclitaxel, docetaxel, cyclophosphamide, eribulin), either as monotherapy or as part of combination therapy.[40] The rationale behind the selection of included therapies was

not indicated. The primary outcome of interest was PFS; overall survival (OS), overall response rate (ORR), clinical benefit rate (CBR), and safety (all-cause discontinuation, discontinuation due to adverse events) were the secondary outcomes of interest, but have not been published.[40] The results of the analyses of secondary outcomes were reviewed by pCODR but have not been summarized in this report.

Multiple databases were searched for evidence (Medline, Embase, Cochrane Library, conference proceedings). The search strategies were provided and were restricted to literature published in 2007 and onward. The selection criteria were applied to the search results by two independent reviewers, with a third reviewer used in the event of discrepancies. The systematic review methods and presentation of search results (before and after applying the eligibility criteria) complied with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines. Eligible trials were assessed for quality (risk of bias) using the Cochrane Collaboration's Risk of Bias tool.

Table 11: Selection criteria of the systematic review.

PICOS Parameter	Inclusion Criteria	Exclusion Criteria
Population	• Women with HR-positive, HER2-negative ABC in first-line setting	• Non HR-positive, HER2-negative subtype, or study does not report PFS outcomes separately for this subtype • Not ABC; or includes mixed population, but does not report PFS results separately for ABC
Interventions and Comparators	• At least one of the following therapies, either as monotherapy or part of combination therapy: o Hormone therapy: letrozole, anastrozole, exemestane, tamoxifen, fulvestrant o Targeted therapy: everolimus, palbociclib, ribociclib, abemaciclib Chemotherapy: capecitabine, doxorubicin, paclitaxel, docetaxel, cyclophosphamide, eribulin[40]	• Does not include a drug of interest
Outcomes	• PFS • OS[40] • ORR[40] • CBR[40] • Safety (all cause discontinuation and discontinuation due to adverse events)[40]	• No PFS outcome reported
Study Design	• RCT	• Observational studies • Single-arm studies • Case reports • Editorials or opinion pieces • Reviews
Abbreviations: ABC – advanced breast cancer; **CBR** – clinical benefit rate; **HR** – hormone receptor; **OS** – overall survival; **PICOS** – Population, Intervention, Comparators, Outcomes and Study Design; **PFS** – progression-free survival; **RCT** – randomized controlled trial.		

Systematic Review Results

The literature search identified 3788 records. After screening, 645 full-text records were assessed for eligibility, and of these, 17 records representing five unique RCTs were included in the systematic review. The trials excluded from the review and the reasons for their exclusion were not identified. The five included trials are summarized in Table 12. Two trials evaluated endocrine therapy with anastrozole and fulvestrant (Mehta, FALCON) and three trials evaluated

endocrine therapy with letrozole combined with targeted therapy (PALOMA-1, PALOMA-2, and MONALEESA-2). No trials of chemotherapy were identified. The sample sizes ranged from 81 to 444 patients among the treatment groups. Upon examination of the baseline characteristics of patients included in the five trials, the pCODR methods team noted variation with respect to ECOG performance status, disease-free interval, and prior therapies, and two trials included a higher proportion of patients with locally advanced disease (PALOMA-2, FALCON).[40] Further, there was a significant amount of missing data for the majority of baseline variables. The quality assessment performed judged the included trials to be "well-conducted with minimal bias";[40] however, from a review of the individual risk of bias assessments, it is clear that for some trials (FALCON, Mehta, PALOMA-2) assessment of specific indicators of trial quality could not be made due to unclear reporting.

Feasibility Assessment of NMA

The feasibility of performing a NMA was primarily based on the availability of data provided by the systematic review results. To be included in the NMA, an outcome had to be reported for at least one trial and for at least one treatment of interest; trials not reporting an outcome were excluded from the analysis of that outcome. Study-level data were extracted from the publications of included trials; the PFS efficacy results of the included trials are presented in Table 13. All five trials provided PFS data amenable to meta-analysis. Median follow-up time ranged from 15.3 months to approximately 30 months among four of the trials reporting median follow-up. Of note, the NMA, as presented in the published conference poster, included interim data from the MONALEESA-2 trial, which is a much shorter duration of follow-up compared to the other three trials. Based on a comparison to the results reported in the conference poster, it appears that the unpublished full report of the NMA included the more mature PFS data (January 2, 2017 data cut-off); however, its inclusion is neither mentioned nor referenced.

Two patient subgroups of interest were pre-specified; these included patients labelled as late progressers and patients with de novo disease. Late progressers were patients who had a disease-free interval ≥12 months from the completion of neo/adjuvant therapy. The definitions used to define de novo disease differed slightly among the trials. In the PALOMA 1 and 2 trials, denovo was defined as patients with no previous systemic therapy and denovo metastases, respectively; while in the FALCON trial, it was defined as patients with no prior exposure to chemotherapies.

Table 12: Baseline patient characteristics of the five trials included in the NMA.[40]

Trials	Mehta 2012		PALOMA-1		PALOMA-2		MONALEESA-2		FALCON	
Treatment Groups	**ANAS**	**ANAS + FULV 250mg**	**PALBO + LET**	**LET**	**PALBO + LET**	**LET**	**RIBO + LET**	**LET**	**ANAS**	**FULV 500mg**
N (ITT, HER2-)	270	266	84	81	444	222	334	334	230	232
Baseline Characteristics										
HR status, %										
ER+, PR+	NR	NR	NR	NR	NR	NR	81	83	76	77
ER+, PR-	NR	NR	NR	NR	NR	NR	NR	NR	19	19
Age, median (range)	NR	NR	63 (54-71)	64 (56-70)	62 (30-98)	61 (28-88)	63 (29-88)	62 (23-91)	64 (38-87)	62 (36-90)
Ethnicity, %										
White	NR	NR	NR	NR	78	78	81	84	76	75
Asian	NR	NR	NR	NR	15	14	8	7	NR	NR
Black	NR	NR	NR	NR	2	1	3	2	NR	NR
Other	NR	NR	NR	NR	6	8	4	2	NR	NR
ECOG PS, %										
0	NR	NR	55	56	58	46	61	61	NR	NR
1	NR	NR	45	44	40	53	39	39	NR	NR
2	NR	NR	0	0	2	1	0	0	NR	NR
>2	NR	NR	0	0	0	0	0	0	NR	NR
Disease stage, %										
Locally advanced	NR	NR	2	1	16	18	0	1	12	14
Metastatic	NR	NR	98	99	31	32	100	99	88	86
No. metastatic sites										
0	NR	NR	NR	NR	0	0	1	0	NR	NR
1	NR	NR	NR	NR	31	30	30	35	NR	NR
2	NR	NR	NR	NR	26	23	35	31	NR	NR
≥3	NR	NR	NR	NR	43	47	34	34	NR	NR
Metastatic site, %										
Bone	NR	NR	NR	NR	NR	NR	74	73	NR	NR
Bone only	NR	NR	20	15	23	22	21	23	NR	NR
Visceral	NR	NR	44	53	48	50	59	59	59	51
Prior therapy, %										
Radiotherapy	NR	NR	NR	NR	NR	NR	53	50	NR	NR
Surgery	NR	NR	NR	NR	NR	NR	100	100	NR	NR
Endocrine therapy	NR	NR	32	35	57	57	NR	NR	NR	NR
Chemotherapy	NR	NR	40	46	48	49	44	43	34	35
Targeted therapy	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Disease-free interval, %										
De novo	NR	NR	52	46	38	37	34	34	NR	NR
≤ 12 months	NR	NR	70	63	22	22	1	10	NR	NR
>12 months	NR	NR	30	37	40	42	65	63	NR	NR
Prior endocrine therapy setting										
Adjuvant	NR	NR	NR	NR	56	57	52	50	NR	NR
Neoadjuvant	NR	NR	NR	NR	NR	NR	0	1	NR	NR
Prior chemotherapy setting										
Adjuvant	NR	NR	NR	NR	41	40	35	38	NR	NR
Neoadjuvant	NR	NR	NR	NR	12	14	12	8	NR	NR

Abbreviations: ANAS – anastrozole; **ECOG** – Eastern Cooperative Oncology Group; **ER** – estrogen receptor; **FULV** – fulvestrant; **HR** – hormone receptor; **ITT** – intent-to-treat; **LET** – letrozole; **NR** – not reported; **PALBO** – palbociclib; **PR** – progesterone receptor; **PS** – performance status; **RIBO** – ribociclib.

Table 13. Progression-free survival outcomes of individual trials included in the NMA.[40]

Trials	Mehta 2012		PALOMA-1		PALOMA-2		MONALEESA-2		FALCON	
Treatment Groups	ANAS	ANAS + FULV 250mg	PALBO + LET	LET	PALBO + LET	LET	RIBO + LET	LET	ANAS	FULV 500mg
N (ITT)	270	266	84	81	444	222	334	334	230	232
Median follow-up	NR		29.6	27.9	23		15.3		25	
PFS										
Median (95% CI)	NR	NR	20.2	10.2	24.8	14.5	22.9	NE	16.6	13.8
HR (95% CI)	0.8 (0.7-1.0)		0.5 (0.3-0.7)		0.6 (0.5-0.7)		0.6 (0.4-0.9)		0.8 (0.6-1.0)	

Abbreviations: ANAS – anastrozole; **CI** – confidence interval; **FULV** – fulvestrant; **HR** – hazard ratio; **ITT** – intent-to-treat; **LET** – letrozole; **PALBO** – palbociclib; **PFS** – progression-free survival; **RIBO** – ribociclib.

NMA Methods

The authors cited using methods consistent with NICE and IPSOR (International Society of Pharmacoeconomics and Outcomes Research). To enable the formation of an evidence network and thus perform the NMA, the endocrine treatment groups that included anastrozole and letrozole were pooled together to form a monotherapy aromatase inhibitors (AI) treatment group; therefore, the analysis assumed equivalence for the two AI. The analysis used Bayesian methods to estimate relative measures of treatment effect. For each pairwise treatment comparison (direct and indirect), hazard ratios (HR) and 95% credible intervals (Crl) were used to measure the association between treatments for efficacy. Ranking probabilities were also estimated and provide the probability that each drug is ranked as having the best efficacy (and second best, and so on) among the available treatments.

In terms of heterogeneity, the possible sources of between study heterogeneity (that is, heterogeneity stemming from differences in study populations, designs, methods, and outcomes etc.) did not appear to be identified or discussed a priori. Both random and fixed effects models were planned to account for possible heterogeneity of treatment effects. Best model fit was determined by comparing the deviance information criterion (DIC) between effects models. Only results of the fixed effect analysis were reported since credible intervals for the random effects model were reported as not estimable. Statistical heterogeneity was assessed using the I^2 metric and Cochran's Q test statistic.

NMA Results

The evidence network for the primary analysis of PFS is shown in Figure 8. The network comprised of five trials (2497 patients), four direct treatment comparisons, with single trials informing three of these comparisons, giving a total of 10 pairwise (direct and indirect) treatment comparisons. The treatments available for comparison were: AI monotherapy, ribociclib plus AI, palbociclib plus AI, fulvestrant 250mg plus AI, and fulvestrant 500mg.

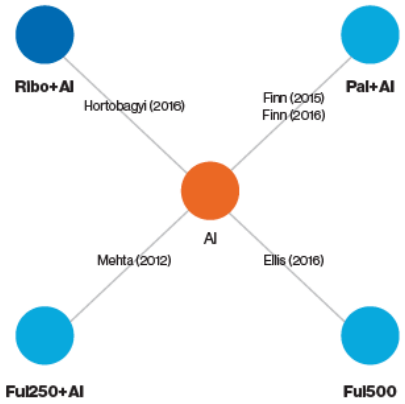


Figure 8: Evidence network for progression-free survival.[10]

Source: full-text conference poster provided by Novartis Pharmaceuticals Canada.

The results of the NMA for PFS are summarized in Table 14. Three treatment regimens (ribociclib plus AI, palbociclib plus AI, fulvestrant 250mg plus AI) demonstrated superior PFS compared to AI monotherapy, with a greater magnitude of benefit observed for the two targeted combination therapies (palbociclib plus AI, HR=0.56, 95% CrI,0.46-0.68; and ribociclib plus AI, HR=0.56, 95% CrI, 0.43-0.72). The targeted combination therapies also showed superior PFS when compared to fulvestrant 250mg plus AI and fulvestrant 500mg (Table 14). When ribociclib plus AI was compared to palbociclib plus AI, no difference in PFS was demonstrated (HR=0.99, 95% CrI, 0.72-1.37). Heterogeneity was deemed non-significant and not present by Cochrane's Q and I^2, respectively (refer to bottom of Table 14). Ribociclib plus AI had the highest probability of being the most efficacious treatment at 51%, followed by palbociclib plus AI at 49%. Incorporating the mature PFS data in the comparison of ribociclib plus AI versus palbociclib plus AI produced an HR of 1.02 (95% CrI, 0.76-1.36).[40]

Table 14: Pairwise treatment comparisons for progression-free survival (primary analysis).[10]

Results show median and 95% CrI of Hazard Ratio (column vs row)

	AI	Ribo+AI	Ful250+AI	Ful500	Pal+AI
AI	1	0.56 (0.43, 0.72)	0.81 (0.67, 0.98)	0.80 (0.63, 1.00)	0.56 (0.46, 0.68)
Ribo+AI	1.80 (1.39, 2.32)	1	1.46 (1.05, 2.01)	1.43 (1.01, 2.02)	1.01 (0.73, 1.39)
Ful250+AI	1.23 (1.02, 1.49)	0.69 (0.50, 0.95)	1	0.98 (0.73, 1.32)	0.69 (0.53, 0.91)
Ful500	1.25 (1.00, 1.58)	0.70 (0.50, 0.99)	1.02 (0.76, 1.37)	1	0.70 (0.52, 0.95)
Pal+AI	1.79 (1.46, 2.18)	0.99 (0.72, 1.37)	1.45 (1.10, 1.90)	1.43 (1.05, 1.92)	1

Notes:

Results reported correspond to the fixed effects model, because this model provided a better fit to the data (DIC of -2.77 and -1.59, respectively for fixed and random effects models). In Pal+AI vs. AI trials, the I^2 was 0.00 and the Q-statistic was 0.49 (p = 0.482).

Source: full-text conference poster provided by Novartis Pharmaceuticals Canada.

Subgroup Analyses

The evidence networks for the subgroup analyses of patients who were late progressers and who had de novo disease are shown in Figures 9 and 10. Results of these analyses are summarized in Tables 15 and 16.

The subgroup analysis of late progressers included two trials (1334 patients), two direct treatment comparisons, with single trials informing each comparison, and giving a total of three pairwise (direct and indirect) treatment comparisons (Figure 9). Both targeted combination therapies demonstrated superior PFS compared to AI monotherapy (Table 15). When ribociclib plus AI was compared to palbociclib plus AI, no difference in PFS was demonstrated (HR=0.96, 95% CrI, 0.68-1.34). Heterogeneity was deemed non-significant and not present in the analysis by Cochrane's Q and I^2, respectively (exact values not reported). In this patient subgroup, ribociclib plus AI had a 60% probability of being the most efficacious treatment, followed by palbociclib plus AI at 40%.

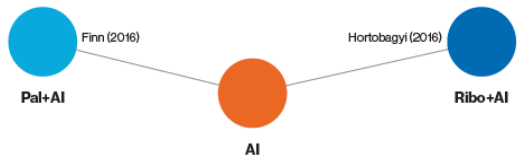


Figure 9: Evidence network for patient subgroup of late progressers.[10]

Source: full-text conference poster provided by Novartis Pharmaceuticals Canada.

Table 15: Pairwise treatment comparisons for progression-free survival in late progressers patient subgroup.[10]

Results show median and 95% CrI of Hazard Ratio (column vs row)

	AI	Ribo+AI	Pal+AI
AI	1	0.56 (0.43, 0.72)	0.58 (0.46, 0.73)
Ribo+AI	1.80 (1.39, 2.33)	1	1.04 (0.74, 1.48)
Pal+AI	1.72 (1.38, 2.16)	0.96 (0.68, 1.34)	1

Source: full-text conference poster provided by Novartis Pharmaceuticals Canada.

The subgroup analysis of patients with de novo disease included four trials (1961 patients), three direct treatment comparisons, with single trials informing all but one comparison, and giving a total of six pairwise treatment comparisons (direct and indirect; Figure 10). Fulvestrant 500mg, ribociclib plus AI, and palbociclib plus AI all showed superior PFS when compared to AI monotherapy. Comparisons of the remaining treatments demonstrated no differences in PFS (Table 16). Heterogeneity was deemed significant/present in the analysis (Cochrane's Q p-value=0.035; I^2=0.78). In this patient subgroup, ribociclib plus AI had the highest probability of being the most efficacious treatment at 71% followed by palbociclib plus AI at 29%.

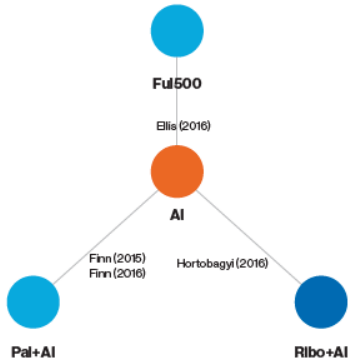


Figure 10: Evidence network for patient subgroup with de novo disease.[10]

Source: full-text conference poster provided by Novartis Pharmaceuticals Canada.

Table 16: Pairwise treatment comparisons for progression-free survival in de novo disease patient subgroup.[10]

Results show median and 95% CrI of Hazard Ratio (column vs row)

	AI	Ribo+AI	Ful500	Pal+AI
AI	1	0.45 (0.27, 0.76)	0.75 (0.58, 0.97)	0.54 (0.39, 0.74)
Ribo+AI	2.21 (1.32, 3.68)	1	1.66 (0.94, 2.93)	1.19 (0.64, 2.16)
Ful500	1.33 (1.03, 1.71)	0.60 (0.34, 1.07)	1	0.71 (0.47, 1.08)
Pal+AI	1.87 (1.35, 2.58)	0.84 (0.46, 1.55)	1.40 (0.93, 2.12)	1

Source: full-text conference poster provided by Novartis Pharmaceuticals Canada.

Conclusions of the NMA

The authors of the NMA concluded that the analyses performed consistently indicated that women with post-menopausal HR-positive, HER2-negative ABC receiving palbociclib plus AI, ribociclib plus AI, or fulvestrant as first-line treatment had longer PFS than those who received AI alone. Further, targeted combination therapies were found to have the highest probability of being the most efficacious among all treatments compared and in all patient subgroups examined.

Critical Appraisal

The quality of the manufacturer-submitted NMA was assessed according to the recommendations made by the ISPOR Task Force on Indirect Treatment Comparisons.[11] Details of the critical appraisal are presented in Table 17.

Table 17. Adapted ISPOR Questionnaire assessing the relevance and credibility of the manufacturer submitted MTC and NMA†

IPSOR Questions†	Details and Comments‡
1. Is the population relevant?	**Yes, in part.** The patients included in trials comprising the NMA evidence network aligned with the target population of interest (HR-positive, HER2-negative previously untreated ABC); however, there is considerable missing data on the HR status of patients (for three of the five trials) considering HR-positive status was an inclusion criterion of all the included trials.
2. Are any critical interventions missing?	**Yes**. The NMA included relevant treatment comparators, however, additional available therapies (exemestane, everolimus, and chemotherapy) could not be included in the primary analysis due to limitations in the structure of the evidence network. In order to enable comparisons to chemotherapy, two separate data sources (a NMA by Generali et al,[41] and a trial by Beck et al),[42] which compared chemotherapy to everolimus-exemestane, were incorporated into the evidence network by way of a sensitivity analysis.
3. Are any critical outcomes missing?	Yes. Relevant outcomes were considered, including PFS, OS, ORR, CBR, and safety outcomes. However, health-related QOL was not listed as an outcome of interest.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Yes.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Unclear**. The systematic review appeared comprehensive in terms of the approach used to search for evidence. However, a detailed list of the specific trials excluded from the review (and reasons for exclusion) was not provided. The pCODR review team is aware of at least one trial that should have been included in the systematic review.[43]
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**Unclear**. The included trials formed a connected network comprising of primarily single trial connections with no closed loop under the assumption of equivalence of anastrozole and letrozole.
7. Is it apparent that poor quality studies were included leading to bias?	**Unclear**. The included trials were assessed for risk of bias using the Cochrane Risk of Bias tool and the results of these assessments were provided. The authors judged the included trials to be "well-conducted with minimal bias"; however, for three of the trials assessment of specific indicators of quality could not be made due to "unclear" reporting.
8. Is it likely that bias was introduced by selective reporting of outcomes in the studies?	**Unclear**. There is a possibility of selective reporting of outcomes since it is unclear whether all available eligible trials were included in the analyses of different outcomes.

IPSOR Questions†	Details and Comments‡
9. Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes**. Differences between the trials in baseline patient characteristics were evident (ECOG performance status, disease stage, disease-free interval) and the amount of missing data precludes an assessment of variation in other important baseline variables (ethnicity, HR status, prior therapy, metastatic sites). Therefore, it is possible that the treatment estimates obtained are biased due to differences in the distributions of treatment effect modifiers between trials and thus treatment groups.
10. If yes (i.e., there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Not reported.**
11. Were statistical methods used that preserve within-study randomization? (i.e. no naïve comparisons)	Yes. Bayesian methods were used for the NMA.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops, was agreement in treatment effects (i.e. consistency) evaluated or discussed?	**Not applicable** (no closed loop).
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Not applicable** (no closed loop).
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias in the analysis?	**No**.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	Yes, in part. Both random and fixed effects model analyses were performed, however, the rationale for performing both analyses was not reported. Only the results of the fixed effect analysis were reported; the authors indicated the fixed effects analysis was preferred based on a better fit to the data (DIC statistic).
16. If random effects model was used, were assumptions about heterogeneity explored or discussed?	**Yes, in part.** The included trials were discussed in terms of enrolling a similar population of patients (HR-positive and HER2-negative status and disease stage); however, there was no discussion or judgment made about other possible sources of heterogeneity (for example, notable variation in ECOG status, disease-free interval, prior therapy; and the significant amount of missing data for a number of variables). Heterogeneity was assessed statistically using the I^2 metric and Cochrane's Q statistic, and these measures detected no heterogeneity in the primary analysis. However, it is likely that the analysis was underpowered to detect statistical heterogeneity since most treatment comparisons were informed by single trials.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Yes, in part.** Two subgroup analyses (de novo disease, late progressers) were pre-specified. Meta-regression adjustments could not be performed due to the low number of included trials in the evidence network.

IPSOR Questions[†]	Details and Comments[‡]
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes.
19. Are the individual study results reported?	Yes.
20. Are the results of direct comparisons reported separately from results of the indirect comparisons or NMA?	Yes.
21. Are all pairwise contrasts between interventions as obtained with the NMA reported along with measures of uncertainty?	Yes.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes.
23. Is the impact of important patient characteristics on treatment effects reported?	**No**.
24. Are the conclusions fair and balanced?	**No.** The conclusions made cannot be considered fair and balanced owing to differences in patient characteristics (treatment effect modifiers) between trial treatment groups and a substantial amount of missing data for important variables, which were unaccounted for in analyses.
25. Were there any potential conflicts of interest?	**Not reported.**
26. If yes, were steps taken to address these?	**Not applicable.**
Abbreviations: ABC – advanced or metastatic breast cancer; **CBR** – clinical benefit rate; **DIC** – deviance information criterion; **ECOG** – Eastern Cooperative Oncology Group; **HER2** – human epidermal growth factor receptor 2; **HR** – hormone receptor; **ITC** – indirect treatment comparison; **NMA** – network meta-analysis; **ORR** – overall response rate; **OS** – overall survival; **PFS** – progression-free survival; **QOL** – quality of life.	
Notes: [†] Adapted from Jansen et al.[11] [†] Bolded comments are considered a weakness of the NMA.	

Limitations and Interpretation

Overall, the reporting of methods used to conduct the systematic review (searches, study selection, data extraction, and critical appraisal) were, for the most part, clear and comprehensive. However, it is possible that not all relevant trials were included in the NMA. The CGP is aware of at least one trial that should have been included in the systematic review (the FACT trial);[43] however, it is unknown if it was considered since a list of excluded trials was not provided.

The validity of a NMA is based on three assumptions: similarity, homogeneity, and consistency. These three constructs refer to whether the included trials were similar enough to consider together; whether the results (treatment effect size) from trials in the same comparison were homogeneous or heterogeneous; and whether the results from direct and indirect comparisons were consistent. The pCODR Methods Team identified concerns related to these three

assumptions, as well as other limitations, which considered together, raised uncertainty about the validity of the treatment estimates obtained. Specifically:

- The patient populations of included trials aligned with the target population of this review (HER2-status, stage of disease, and first-line treatment of ABC); however, there were considerable missing data on the HR status of patients (data were missing for three of five trials). This was surprising considering HR-positive status was an inclusion criterion of all the included trials. Nonetheless, considering the missing data, it's important to note that the analysis was clearly based on the assumption that all included patients had HR-positive status.
- Visual inspection of the distribution of important baseline patient characteristics (treatment effect modifiers) across the five included trials showed significant variability in regards to ECOG performance status, disease-free interval, and disease stage. Furthermore, there was a substantial amount of missing data for other important variables (HR status, ethnicity, prior therapy, and metastatic sites). Given the degree of heterogeneity present and the amount of missing data, it is questionable whether it is appropriate to deem the trials similar enough to be compared in a NMA.
- Heterogeneity could not be explored using meta-regression analyses due to the small number of included trials in the evidence network (n=5). The authors reported that both random and fixed effects analyses were performed in order to account for different assumptions relating to heterogeneity; but only results of the fixed effect analysis were reported. This is appropriate given the small number of trials. However, when heterogeneity is present (as noted above) and a fixed effect model is applied, uncertainty intervals (95% credible intervals) become artificially narrow, which incorrectly implies greater certainty about the estimated treatment effect.[44] Further, when the number of trials informing treatment comparisons is low (most treatment comparisons in the evidence network were informed by single trials) a fixed effect model analysis has limited power to detect statistical heterogeneity. In the primary analysis of PFS, heterogeneity was deemed not present and non-significant for all treatment comparisons by means of the I^2 and Cochrane's Q statistics, respectively. In consideration of these limitations, and the fact that the primary analysis did not adjust for differences between trials in important treatment effect modifiers, it is likely that the treatment effect estimates obtained are biased and not solely due to the effects of the treatments examined.
- Due to the structure of the evidence network (no closed loop), the consistency between direct and indirect comparisons could not be assessed.
- Other available treatments including chemotherapy, exemestane, and everolimus, could not be included in the primary analysis of PFS due to constraints in the structure of the evidence network. This limits the usefulness of the NMA since not all contemporary treatments were included. In an effort to address this limitation, the authors did perform a sensitivity analysis (which was only reported in the unpublished full NMA report) incorporating trial data from two sources external to the systematic review performed (an NMA by Generali et al,[41] and a trial by Beck et al[42]), which both compared chemotherapy to everolimus-exemestane. Information on the nature and quality of these addition data sources was lacking and prevented an adequate appraisal of the sensitivity analysis. Further, the relevance of chemotherapy as a comparator is questionable as the CGP indicated that chemotherapy is usually reserved for post-endocrine therapy failure.
- The results of subgroup analyses should be interpreted with caution as they are likely underpowered to detect differences between treatment groups, and for the de novo disease patient subgroup, the definitions used to categorize patients differed among the included trials.

- While not a limitation, it should be noted that probability rankings should be interpreted in relation to the overall statistical significance of the results obtained. Therefore, attributing a treatment has the highest probability of being the most efficacious treatment is inappropriate when the overall result of the comparison is not significant.
- The NMA was funded and performed by a consultancy group hired by the Manufacturer and therefore the results should be interpreted considering this conflict of interest and a lack of peer review.

Summary

The Manufacturer submitted a NMA comparing ribociclib-letrozole to other available endocrine-based therapies as first-line treatment in post-menopausal women with HR-positive and HER2-negative ABC. Results of the NMA have been published (conference poster) for the primary outcome of PFS,[10] and were critically appraised by the pCODR Methods Team according to the recommendations of the IPSOR Task Force on Indirect Treatment Comparisons.[11] The methods used to perform the systematic review informing the NMA were, for the most part, clear and comprehensive. However, it is possible that not all relevant trials were included. For an NMA to be feasible, the authors assumed equivalence of letrozole and anastrozole, combining these treatments into an AI monotherapy treatment group. The NMA included five trials and five treatments available for comparison: AI monotherapy, ribociclib plus AI, palbociclib plus AI, fulvestrant 250mg plus AI, and fulvestrant 500mg. The patient populations of the trials aligned with the target population of this review (HER2-status, stage of disease, and first-line treatment of ABC); however, variation in the distribution of important baseline patient characteristics (treatment effect modifiers) was apparent and there was a substantial amount of missing data for other important variables. Considering these limitations, it is questionable whether it was appropriate to deem the trials similar enough to be compared in a NMA. Heterogeneity could not be explored using meta-regression analyses due to the small number of included trials, and therefore, unadjusted analysis results were reported based on a fixed effects analysis. The results of the NMA primary analysis indicated longer PFS with ribociclib plus AI, palbociclib plus AI, and fulvestrant compared to AI monotherapy, and no difference in PFS between ribociclib plus AI and palbociclib plus AI. Since the primary analysis did not adjust for differences between trials in important treatment effect modifiers, it is likely that the treatment effect estimates obtained in the NMA are biased and not solely due to the effects of the treatments examined, and therefore, should be interpreted with caution.

7.2 Critical appraisal of the Manufacturer's submitted indirect treatment comparison (ITC) and matching-adjusted indirect treatment comparison (MAIC) of ribociclib-letrozole and palbociclib-letrozole as first-line treatment in HR-positive, HER2-negative ABC

7.2.1 Objective

The objective of this section is to summarize and critically appraise the methods and results of the manufacturer-submitted ITC and MAIC comparing ribociclib-letrozole to palbociclib-letrozole, as first-line treatment in post-menopausal women with HR-positive and HER2-negative ABC, in order to inform the pCODR clinical and economic evaluations of ribociclib-letrozole to relevant comparators. Results of the ITC and MAIC have been published (conference poster) for the primary outcome of progression-free survival (PFS), and for overall survival (OS) and grade 3/4 adverse events (AE).[12] The appraisal was also informed by unpublished information provided by the Submitter in the form of an ITC and MAIC full report.[45]

7.2.2 Findings

Rational and Objectives
Indirect treatment comparisons can lead to biased results due to differences in cross-trial patient populations, trial design, and outcome definitions. If available for at least one treatment of interest, the use of individual patient data (IPD) can address the limitations of classic ITC by correcting for cross-trial differences through adjustment of IPD to match the baseline characteristics of patients included in comparator trials with published summary data. Treatment outcomes are then compared between treatment groups. MAIC methods were used to compare ribociclib-letrozole with palbociclib-letrozole in order to derive relative estimates of treatment effect and use them a supportive evidence for the pCODR submission.

Scope
Individual patient data were available for the phase 3 MONALEESA-2 trial. The scope of the analysis was to compare ribociclib-letrozole to palbociclib-letrozole using unadjusted (ITC) and adjusted (MAIC) methods for the analysis of PFS, OS, and grade 3/4 AE.

Systematic Review
It was reported that relevant trials were identified through a systematic literature search that followed the methods of the Cochrane Collaboration and NICE;[45] however, important details of the review process (selection criteria, search strategies, sources searched) were not specified. Consequently, the number and specific treatments considered for inclusion into review (and analysis) is unclear. It was mentioned briefly in the unpublished full report that trials evaluating fulvestrant alone or in combination with anastrozole were considered for inclusion but were ultimately excluded based on the inability to link these regimens to other treatments in the evidence network.[45]

Systematic Review Results
The reporting and presentation of the systematic review results did not conform to PRISMA. It was reported that the search identified one trial evaluating ribociclib-letrozole (MONALEESA-2) and two trials evaluating palbociclib-letrozole (PALOMA-2 and PALOMA-1). The total number of trials identified by the literature search and the number of trials excluded from the review were not

reported. The included trials and the source of trial data used in analyses are summarized in Table 18. Efficacy and safety outcomes of the individual trials are summarized in Table 19.

Table 18: Trial data used in the ITC and MAIC.[45]

Trial	Treatment Comparison	Data Source	Data cut-off date/Publication	No. Patients
MONOLEESA-2	Ribociclib-letrozole vs. placebo letrozole	IPD	1st data cut-off: January 19, 2016[a] 2nd data cut-off: January 4, 2017	334 vs. 334
PALOMA-2	Palbociclib-letrozole vs. placebo-letrozole	Published summary data	Finn et al, NEJM, 2016	444 vs. 222
PALOMA-1	Palbociclib-letrozole vs. letrozole	Published summary data	Finn et al, Lancet Oncol, 2015	84 vs. 81
Abbreviations: IPD – individual patient data; **vs.** versus.				
Notes: [a] – Publication was trial clinical study report.				

Table 19: Published efficacy and safety outcomes of individual trials included in the ITC and MAIC.[45]

Trial, comparison	N	Median Follow-up in months	PFS, median HR (95% CI)	OS, median (HR (95% CI)	Grade AE, n (%)
MONALEESA-2 Ribociclib-letrozole vs. placebo-letrozole	334 vs. 334	15.3[a]	NR vs. 14.7 0.56 (0.43-0.72)	NR vs. NR 1.28 (0.62-2.1)	271 (81.1) vs. 108 (32.7) RR=2.51[c]
		~28[b]	25.3 vs. 16 0.57 (0.46-0.70)	NR vs. 33 0.75 (0.52-1.08)	
PALOMA-2 Palbociclib-letrozole vs. placebo-letrozole	444 vs. 222	23	24.8 vs. 14.5 0.58 (0.46-0.72)	NR	336 (75.7) vs. 54 (24.3) RR=3.11
PALOMA-1 Palbociclib-letrozole vs. letrozole	84 vs. 81	29.6	20.2 vs. 10.2 0.49 (0.32-0.75)	37.5 vs. 33.3 0.81 (0.49-1.35)	63 (75) vs. 65 (80.2)
Abbreviations: AE – adverse events; **CI** – confidence interval; **HR** – hazard ratio; **NA** – not available; **NR** – not reached; **vs.** versus; **RR** – relative risk.					
Notes: [a] – Median follow-up time at first data cut-off date. [b] – Median follow-up time at second data cut-off date. [c] – Assessed in the safety population (n=664).					

Matching Feasibility Assessment[45]

In order to determine the feasibility of performing a MAIC analysis, the inclusion/exclusion criteria, stratification variables, baseline characteristics of included patients, and the outcomes reported in each trial were reviewed and compared. While the inclusion and exclusion criteria used in the trials were judged to be very similar, the variables used to stratify patients were quite different. The MONALEESA-2 trial stratified patients based on the presence of liver and/or lung metastases, and the palbociclib-letrozole trials stratified by disease site and disease-free interval. No significant differences between the trials, with respect to baseline patient characteristics, were noted by the authors; however, upon examination, the pCODR Methods Team observed some variation among the three trials with respect to ECOG performance status and disease-free interval, as well as missing data in the PALOMA trials for histology, extent of disease/metastatic sites, and prior therapy. Based

on their review of available data from the published trial reports, the authors concluded that the MONALEESA-2 and both PALOMA trials were comparable to analyze in a MAIC with limited transitivity bias, which means the trials were deemed sufficiently similar in all respects other than the treatments being compared. They noted that indications for treatment were identical between the trials and the placebo groups were similar in dosing and outcomes.

The matching feasibility assessment was presented as a list of 23 variables with an indication for each trial, based on available data, whether matching on each variable was possible, not possible, or required exclusion of a patient subgroup. The rationale for the selection of the 23 variables, however, was not provided. A request for this information was made by the pCODR Methods Team to the Manufacturer, who indicated that the following criteria were used for selecting variables for matching:

- Data availability in the trials
- Based on the feasibility assessment, there was an imbalance between treatment groups and therefore a potential imbalance between trials
- Variables considered are potential effect modifiers or confounding factors

Variables meeting the above criteria were included as matched variables in analyses. For the analysis of PFS, the PALOMA -2 trial was selected as the base case trial to match and included the following variables: age, race, ECOG performance status, chemotherapy and hormonal setting, disease stage at initial diagnosis, number of metastases, disease-free interval and visceral metastases.[12] The Manufacturer confirmed there was no imbalance in HR and HER2 status between the trials; therefore, these variables were not selected for matching.[4]

A different set of matched variables were used for the analysis of OS since this analysis required matching to the PALOMA-1 trial (OS data were not available for PALOMA-2).[12] The phase 2 design of PALOMA-1 limited the number of variables available for matching. Considering this limitation and the immaturity of the MONALEESA-2 OS data (too few deaths to reliably compare OS between treatments), the authors deemed the OS MAIC analysis exploratory in nature. The matched variables for the OS analysis included the following: age, ECOG performance status, disease-free interval and visceral metastases.[12]

Finally, the authors identified a few important treatment effect modifiers that could not be included in either of the MAIC analyses due to unavailable data in the PALOMA trials; these included histology, extent of disease/metastatic sites, and any prior therapy (surgery, radiotherapy, and medication setting).[12]

ITC and MAIC Methods

ITC

Classic frequentist ITC was performed using the methods of Bucher to compare the treatment efficacy of ribociclib-letrozole relative to palbociclib-letrozole, and obtain estimates of treatment effect.[12] For the analysis of PFS and OS, hazard ratios (HR) were reported with 95% confidence intervals (CI); and for the analysis of safety (grade 3/4 AEs), risk ratios (RR) and 95% CI were reported.[12] The type of effects model used in analyses was not specified. The ITC analyses were unadjusted for any differences in treatment effect modifiers between trials (and thus treatment groups).

MAIC

After identification of the variables to be used for matching, the MAIC analysis involved weighting the ribociclib-letrozole IPD, such that the means/percentages of patient characteristics common to both trials matched the comparator trial data (PALOMA-2 for PFS, and PALOMA-1 for OS).[12] Logistic regression analysis was used to generate weights (propensity scores) for the IPD. For PFS and OS,

adjusted HR and 95 CI were calculated using weighted Cox regression models, and frequentist ITC was performed after matching adjustment.[12] The MAIC did not include an analysis of grade 3/4 AE as safety outcomes are unlikely linked to baseline characteristics.

ITC and MAIC Results[12]

The evidence network for ITC and MAIC comprised of three trials (MONALEESA-2, PALOMA-2, and PALOMA-1), which included two direct comparisons (ribociclib-letrozole vs. placebo-letrozole; palbociclib-letrozole vs. placebo-letrozole) and one indirect comparison (ribociclib-letrozole vs. palbociclib-letrozole). The results of the ITC and MAIC are presented in Table 20, and summarize comparisons using data from the second data cut-off date of the MONALEESA-2 trial.

For PFS, results of the unadjusted ITC showed superior PFS efficacy with both targeted combination therapies when compared to placebo-letrozole (Table 20). Although the direction of treatment effect appears to favour ribociclib-letrozole, no statistically significant difference in PFS was demonstrated between ribociclib-letrozole and palbociclib-letrozole in the unadjusted analysis (HR=0.98, 95% CI, 0.72-1.34). The MAIC analysis of PFS showed a similar result to the ITC analysis, producing an adjusted HR of slightly greater magnitude (HR=0.90, 95% CI, 0.64-1.27).

For the exploratory analysis of OS, results of the unadjusted ITC showed no statistically significant differences in OS between any of the treatments compared. The unadjusted HR for the comparison of ribociclib-letrozole to palbociclib-letrozole was 0.92 (95% CI, 0.49-1.71). The MAIC analysis demonstrated similar findings, producing an adjusted HR of slightly greater magnitude (HR=0.84, 95% CI, 0.44-1.60).

For the analysis of safety, results of the ITC demonstrated that the risk of grade 3/4 AE was significantly lower with placebo-letrozole compared to either targeted combination therapy. For the comparison of ribociclib-letrozole versus palbociclib-letrozole, the ITC yielded a relative risk ratio of 0.75 (95% CI, 0.57-0.99), which favoured ribociclib-letrozole.

Table 20: Results of ITC and MAIC for progression-free survival, overall survival and grade 3/4 adverse events.[12]

Comparison	Ribociclib-letrozole* vs. placebo-letrozole	Palbociclib-letrozole vs. placebo-letrozole	Ribociclib-letrozole* vs. palbociclib-letrozole
Outcomes			
PFS[a]	**HR (95% CI)**		
ITC	0.57 (0.46-0.70)[45]	0.58 (0.46-0.72)	0.98 (0.72-1.34)[45]
MAIC[b]	0.52 (0.41-0.68)[45]	0.58 (0.46-0.72)	0.90 (0.64-1.27)[45]
OS (exploratory)[c]	**HR (95% CI)**		
ITC	0.75 (0.52-1.08)	0.81 (0.49-1.35)	0.92 (0.49-1.71)
MAIC[d]	0.68 (0.46-1.02)	0.81 (0.49-1.35)	0.84 (0.44-1.60)
Grade 3/4 AE[a]	**RR (95% CI)**		
ITC	2.34 (2.02-2.71)[45]	3.11 (2.45-3.95)[45]	0.75 (0.57-0.99)[45]
Abbreviations: AE – adverse events; **CI** – confidence interval; **HR** – hazard ratio; **ITC** – indirect treatment comparison; **MAIC** – matching-adjusted indirect comparison; **RR** – relative risk; **OS** – overall survival; **vs.** versus.			
Notes: * **-** Analyses used data from the second data cut-off date of January 4, 2017.[45] [a] –Trial data used in comparisons were from PALOMA-2. [b] – Analyses adjusted through matching on the following variables: age, race, ECOG status, chemotherapy and hormonal setting, disease stage at initial diagnosis, number of metastases, disease-free interval, and visceral metastases. [c] – Trial data used in comparisons were from PALOMA-1. [d] – Analyses adjusted through matching on the following variables: age, ECOG performance status, disease-free interval and visceral metastases.			

Conclusions of the ITC and MAIC

Using ITC and MAIC resulted in treatment effect estimates that slightly favoured ribociclib-letrozole over palbociclib-letrozole for PFS and OS, but the results were not statistically significant. The findings suggest ribociclib-letrozole may be more efficacious compared to palbociclib-letrozole. The ITC demonstrated that the risk of grade 3/4 AE was significantly lower with placebo-letrozole compared to either targeted combination therapy. The risk of grade 3/4 AE marginally favoured ribociclib-letrozole compared to palbociclib-letrozole.

Critical Appraisal

The quality of the manufacturer-submitted ITC was assessed according to the recommendations made by the ISPOR Task Force on Indirect Treatment Comparisons.[11] Details of the critical appraisal are presented in Table 21. As previously noted in section 7.1.2, the validity of an ITC is based on the assumptions of similarity, homogeneity, and consistency (refer to section 7.1.2 for explanations of these constructs).

Table 21. Adapted ISPOR Questionnaire assessing the relevance and credibility of the manufacturer submitted ITC.

IPSOR Questions†	Details and Comments‡
1. Is the population relevant?	Yes. The patients included in trials comprising the evidence network aligned with the target population of interest (HR+, HER2- previously untreated ABC).
2. Are any critical interventions missing?	**Yes**. The ITC compared two treatments, ribociclib-letrozole to palbociclib-letrozole; additional available therapies (anastrozole, exemestane, fulvestrant, everolimus, and chemotherapy) were not included in the analysis. Since details of the systematic review were not reported, it is unclear how many treatments were initially considered for inclusion into the analysis.
3. Are any critical outcomes missing?	Yes. Relevant outcomes were considered, including PFS, OS, and safety. Health-related QOL, however, was not listed as an outcome of interest.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Yes.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Unclear.** Important details of the systematic review that was performed were not included in the report provided to pCODR, including trial selection criteria, eligible treatments, and a list of the trials excluded from the review (with reasons for exclusion).
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes. The included trials formed a connected network comprising of single trial connections with no closed loop.
7. Is it apparent that poor quality studies were included leading to bias?	**No, in part**. It is unknown if the included trials were assessed for risk of bias as part of the systematic review performed. However, the pCODR methods team's independent review and appraisal of the included trials (MONALEESA-2 and PALOMA-2) supports their inclusion in the primary analysis of PFS based on a low risk of bias in either trial. For the analysis of OS, however, the inclusion of the PALOMA-1 trial may lead to biased estimates of this outcome (this trial has design and conduct features associated with a higher risk of bias). Appropriately, based on several limitations, the OS analysis was deemed exploratory.

IPSOR Questions†	Details and Comments‡
8. Is it likely that bias was introduced by selective reporting of outcomes in the studies?	No.
9. Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes.** Differences between the trials in baseline patient characteristics were observed (ECOG performance status, disease-free interval), and other differences are possible considering missing data for a number of variables in the PALOMA trials (histology, extent of disease/metastatic sites, and prior therapy). Therefore, it is possible that the treatment estimates obtained may be confounded due to differences in the distributions of treatment effect modifiers between trials.
10. If yes (i.e., there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Not reported.**
11. Were statistical methods used that preserve within-study randomization? (i.e. no naïve comparisons)	Yes, ITC was performed using the Bucher method.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops, was agreement in treatment effects (i.e. consistency) evaluated or discussed?	**Not applicable** (no closed loop).
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Not applicable** (no closed loop).
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias in the analysis?	**No.**
15. Was a valid rationale provided for the use of random effects or fixed effect models?	**No.** The type of analysis performed, fixed versus random effects, was not reported.
16. If random effects model was used, were assumptions about heterogeneity explored or discussed?	**Unknown.**
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression	**No**.

IPSOR Questions†	Details and Comments‡
analysis with pre-specified covariates performed?	
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes.
19. Are the individual study results reported?	Yes.
20. Are the results of direct comparisons reported separately from results of the indirect comparisons or NMA?	Yes.
21. Are all pairwise contrasts between interventions as obtained with the NMA reported along with measures of uncertainty?	Yes.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	No.
23. Is the impact of important patient characteristics on treatment effects reported?	No.
24. Are the conclusions fair and balanced?	Yes, overall, the conclusions are considered fair and balanced based on the reported results of the ITC.
25. Were there any potential conflicts of interest?	**Not reported.**
26. If yes, were steps taken to address these?	**Not applicable.**
Abbreviations: ABC – advanced or metastatic breast cancer; **ECOG** – Eastern Cooperative Oncology Group; **HER2** – human epidermal growth factor receptor 2; **HR** – hormone receptor; **ITC** – indirect treatment comparison; **OS** – overall survival; **PFS** – progression-free survival; **QOL** – quality of life.	
Notes: † Adapted from Jansen et al.[11] ‡ Bolded comments are considered a weakness of the ITC.	

The methods performed for the MAIC were also compared against best practice principles for performing MAIC, outlined by Signorovitch et al (2012),[13] which combines IPD for one or more treatments with published summary data for comparator treatments.

Limitations and Interpretation

The patient populations of the two trials included in the primary analysis of PFS (MONALEESA-2 and PALOMA-2) aligned with the target population of this review (HER2-status, stage of disease, and first-line treatment of ABC), and were very similar in terms of trial design, baseline patient characteristics, and outcomes. Upon review, the pCODR Methods Team did not identify any concerning differences in the distributions of known treatment effect

modifiers between the trials. Therefore, the pCODR Methods Team considered an ITC of the trials to be appropriate.

The integrity of any data synthesis is based on the premise that a systematic review has been performed and all relevant trials have been identified and included (or considered for inclusion) into the data analysis. Very little information, however, was reported on the systematic review that was undertaken to identify trials for the ITC and MAIC. Important details of the review process (selection criteria, search strategies, risk of bias assessment) were not specified, and therefore, it is unclear how many treatments (and thus trials) were considered and excluded from the review. Further, some aspects of the ITC analysis (effects model used) were also lacking. The sub-optimal reporting of methods in these areas undermines the analysis performed.

The scope of the ITC and MAIC is limited to one treatment comparator: palbociclib-letrozole. While the pCODR Methods Team acknowledges this may be the most relevant treatment comparator, the analyses do not address the relative efficacy of ribociclib-letrozole to other available treatments (anastrozole, fulvestrant, exemestane, everolimus, and chemotherapy).

Despite the limitations noted above, the pCODR Methods Team still considered the credibility (interval validity) of the PFS analysis of the ITC and MAIC to be adequate. This judgement was based on the low risk of bias associated with the individual trials, the similarity of the trials being compared, a perceived low risk of confounding of the treatment effect (via imbalances in known treatment effect modifiers between trials), use of analysis techniques that comply with best practice, and the consistency of the results (treatment effect) obtained by the two methods of analysis.

Some additional limitations of the ITC and MAIC analyses and considerations for interpreting the results were identified, and are summarized below:

- The authors did not provide a clear rationale or explanation for the selection of specific variables used for matching. Clarification from the manufacturer, however, indicated that they did indeed carefully select variables based on a set of criteria that included availability of data, demonstrated imbalance between trials/treatment groups, and known treatment effect modifiers or confounders. The authors supplied a comparison of baseline characteristics between the trials (MONALEESA-2 and PALOMA-2) pre- and post-matching, which indicated successful matching was obtained for the analysis. However, it also highlighted that the distributions of matched variables were very similar between the trials pre-matching and, therefore, for the analysis of PFS, it is questionable whether much was gained by performing a MAIC. Comparison of the treatment estimates obtained by ITC and MAIC show similar results, where precision in the estimate (95% CI) is just slightly better with ITC, likely because it is based on more patients (matching on variables reduced the sample to 66% and 71% of the ITT population for the MONALEESA-2 and PALOMA-2 trials, respectively).
- A few important treatment effect modifiers could not be included in the ITC and MAIC analyses performed due to unavailable data in the PALOMA trials; these included histology, extent of disease/metastatic sites, and any prior therapy (surgery, radiotherapy, and medication setting). Consequently, it is possible that the estimates obtained may be confounded since these known treatment effect modifiers were not controlled for in analyses. The same holds true for any unknown cross-trial differences.
- In their cross-trial comparison to identify differences between trials, it is unclear if the authors considered differences related to outcome definitions and assessment (investigator versus independent review), which can also introduce variation across trials.

- The OS analysis of the ITC and MAIC had a number of limitations and therefore the analyses were considered exploratory by the authors. Consequently, the results of these analyses should be interpreted with caution. The specific limitations included the following:
    - The ITC and MAIC of OS made comparisons to a different trial, (phase 2 PALOMA-1), which has design and conduct features associated with a higher risk of bias.
    - The MAIC of OS used fewer variables for matching as a result of using the PALOMA-1 trial; therefore, fewer treatment effect modifiers were controlled for in the analysis (as compared to the PFS analysis).
    - The OS data were considered immature in both of the included trials.
- Due to the structure of the evidence network (no closed loop), the consistency between direct and indirect comparisons could not be assessed.
- The ITC and MAIC was funded and performed by a consultancy group hired by the Manufacturer and therefore the results should be interpreted considering this conflict of interest and a lack of peer review.

Summary

The Manufacturer submitted an ITC and MAIC comparing ribociclib-letrozole to palbociclib-letrozole, as first-line treatment in post-menopausal women with HR-positive and HER2-negative ABC. Results of the ITC and MAIC have been published (conference poster) for the primary outcome of PFS, OS and grade 3/4 AE,[12] and were critically appraised by the pCODR Methods Team according to the recommendations of the ISPOR Task Force on Indirect Treatment Comparisons and best practice principles for MAIC.[11, 13] Very little information was reported on the systematic review that was performed to identify trials for the ITC and MAIC, and therefore, it is unclear how many treatments (and thus trials) were considered and excluded from the analyses. The scope of the primary analysis of PFS was limited to two trials and one treatment comparator: palbociclib-letrozole; therefore, the analyses did not address the relative efficacy of ribociclib-letrozole to other available treatments. The results of the ITC and MAIC were consistent, and showed treatment effect estimates that favoured ribociclib-letrozole over palbociclib-letrozole for PFS, however the difference between treatments was not statistically significant. The ITC demonstrated the risk of grade 3/4 AE was significantly lower with placebo-letrozole compared to either targeted combination therapy. The risk of grade 3/4 AE marginally favoured ribociclib-letrozole compared to palbociclib-letrozole. The pCODR Methods Team considered the internal validity of the PFS analysis for the ITC and MAIC to be adequate. This judgement was based on the low risk of bias associated with the individual trials, the similarity of the trials being compared, a perceived low risk of confounding of the treatment effect (via imbalances in known treatment effect modifiers between trials), use of analysis techniques that comply with best practice, and the consistency of the results (treatment effect) obtained by the two methods of analysis. The OS analysis of the ITC and MAIC had a number of limitations and therefore the results should be interpreted with caution.

8 COMPARISON WITH OTHER LITERATURE

No comparisons with other literature were addressed in this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Breast Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on ribociclib for advanced or metastatic breast cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH 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 Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines.

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

The Breast Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

Refer to Appendix B for more details on literature search methods

1. **Literature search via OVID platform**

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials September 2017, Embase 1974 to 2017 October 25, Ovid MEDLINE(R) ALL 1946 to October 25, 2017

#	Searches	Results
1	(Kisqali* or ribociclib* or LEE-011* or LEE011* or LEE-11* or LEE11* or TK8ERE8P56 or 1211441-98-3 or 1374639-75-4).ti,ab,ot,kf,kw,hw,rn,nm.	549
2	1 use medall	109
3	1 use cctr	49
4	*Ribociclib/ or (Kisqali* or ribociclib* or LEE-011* or LEE011* or LEE-11* or LEE11*).ti,ab,kw.	347
5	4 use oemezd	201
6	5 not conference abstract.pt.	90
7	5 and conference abstract.pt.	111
8	limit 7 to yr="2012 -Current"	110
9	2 or 3 or 6 or 8	358
10	limit 9 to english language	351
11	remove duplicates from 10	249

2. **Literature search via PubMed**

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#4	Search #1 AND #2 Filters: English	10
#3	Search #1 AND #2 Sort by: PublicationDate	10
#2	Search publisher[sb] Sort by: PublicationDate	533362
#1	Search Kisqali*[tiab] OR ribociclib*[tiab] OR LEE-011*[tiab] OR LEE011*[tiab] OR LEE-11*[tiab] OR LEE11*[tiab] OR TK8ERE8P56[tiab] Sort by: PublicationDate	84

3. **Cochrane Central Register of Controlled Trials (Central)**

Searched via Ovid

4. **Grey Literature search via:**

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Kisqali/ribociclib, breast cancer

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Kisqali/ribociclib, breast cancer

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
http://oncologypro.esmo.org/Meeting-Resources

Search: Kisqali/ribociclib, breast cancer - last 5 years

APPENDIX B: DETAILED METHODOLOGY OF LITERATURE REVIEW

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (September 2017) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Kisqali/ribociclib.

No filters were applied to limit the retrieval by study type. The search was limited to English-language documents, but not limited by publication year.

The search is considered up to date as of February 26, 2018.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the San Antonio Breast Cancer Symposium (SABCS) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

REFERENCES

1. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med [Internet]. 2016 Nov 3 [cited 2018 Feb 23];375(18):1738-48. Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa1609709

2. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Kisqali (ribociclib) [Internet]. London (GB): European Medicines Agency; 2017 Jun 22. [cited 2018 Feb 23]. (European public assessment report). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004213/WC500233999.pdf

3. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib + letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Poster presented at: American Society of Clinical Oncology Annual Meeting; 2017 Jun 2-6; Chicago (IL).

4. pan-Canadian Oncology Drug Review manufacturer submission: Kisqali (ribociclib), 200mg tablets. Company: Novartis Pharmaceuticals. Dorval (PQ): Novartis Pharmaceuticals Canada; 2017 Oct 17.

5. Verma S, O'Shaughnessy J, Burris HA, Campone M, Alba E, Chandiwana D, et al. Health-related quality of life of postmenopausal women with hormone receptor-positive human epidermal growth factor receptor 2-negative advanced breast cancer treated with ribociclib + letrozole: results from MONALEESA-2. Poster presented at: American Society of Clinical Oncology Annual Meeting; 2017 Jun 2-6; Chicago (IL).

6. Janni W, Burris HA, Blackwell KL, Hart LL, Chan A, Nusch A, et al. First-line ribociclib + letrozole for postmenopausal women with HR+, HER2- ABC: MONALEESA-2 safety results. Poster presented at: American Society of Clinical Oncology Annual Meeting; 2017 Jun 2-6; Chicago (IL).

7. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer [supplementary appendix]. N Engl J Med [Internet]. 2016 Nov 3 [cited 2018 Feb 23];375(18):1738-48. Available from: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1609709/suppl_file/nejmoa1609709_appendix.pdf

8. Montori VM, Devereaux PJ, Adhikari NK, Burns KE, Eggert CH, Briel M, et al. Randomized trials stopped early for benefit: a systematic review. JAMA. 2005 Nov 2;294(17):2203-9.

9. Schulz KF, Grimes DA. Multiplicity in randomised trials II: subgroup and interim analyses. Lancet. 2005 May 7;365(9471):1657-61.

10. Ayyagari R, Tang D, Patterson-Lomba O, Zhou Z, Xie J, Niravath PA. Progression-free survival (PFS) with first-line endocrine-based therapies among postmenopausal women with HR+/ HER2- metastatic breast cancer: a systematic literature review and network meta-analysis. Poster presented at: AMCP Managed Care & Specialty Pharmacy Annual Meeting 2017; 2017 Mar 27-30; Denver (CO).

11. Jansen JP, Trikalinos T, Cappelleri JC, Daw J, Andes S, Eldessouki R, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health [Internet]. 2014 Mar [cited 2018 Mar 2];17(2):157-73. Available from: https://www.sciencedirect.com/science/article/pii/S1098301514000126

12. Tremblay G, Chandiwana D, Dolph M, Forsythe A, Monaco M. Matching-adjusted indirect treatment comparison of ribociclib and palbociclib as first-line treatments for HR+, HER2- ABC. Poster presented at: European Society for Medical Oncology Annual Meeting; 2017 Sep 8-12; Madrid (ES).

13. Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value Health [Internet]. 2012 Sep [cited 2018 Mar 2];15(6):940-7. Available from: https://www.sciencedirect.com/science/article/pii/S1098301512016105

14. Novartis Pharmaceuticals. Adjuvant Ribociclib With Endocrine Therapy in Hormone Receptor+/HER2- High Risk Early Breast Cancer (EarLEE-1). 2017 Mar 13 [cited 2018 Mar 1]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT03078751 NLM Identifier: NCT03078751.

15. Novartis Pharmaceuticals. Adjuvant Ribociclib With Endocrine Therapy in Hormone Receptor+/HER2- Intermediate Risk Early Breast Cancer (EarLEE-2). 2017 Mar 16 [cited 2018 Mar 1]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT03081234 NLM Identifier: NCT03081234.

16. Novartis Pharmaceuticals. Study of Efficacy and Safety of LEE011 in Men and Postmenopausal Women With Advanced Breast Cancer. (MONALEESA-3). 2015 Apr 21 [cited 2018 Mar 1]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02422615 NLM Identifier: NCT02422615.

17. Fasching PA, Jerusalem GHM, Pivot X, Martin M, De Laurentiis M, Blackwell KL, et al. Phase III study of ribociclib (LEE011) plus fulvestrant for the treatment of postmenopausal patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (aBC) who have received no or only one line of prior endocrine treatment (ET): MONALEESA-3. J Clin Oncol [Internet]. 2016 [cited 2017 Nov 16];34(15 Suppl). Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.TPS624

18. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer [protocol]. N Engl J Med [Internet]. 2016 Nov 3 [cited 2018 Feb 23];375(18):1738-48. Available from: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1609709/suppl_file/nejmoa1609709_protocol.pdf

19. Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2017 [Internet]. Toronto (ON): Canadian Cancer Society; 2017 Jun. [cited 2017 Nov 25]. Available from: http://www.cancer.ca/~/media/cancer.ca/CW/publications/Canadian%20Cancer%20Statistics/Canadian-Cancer-Statistics-2017-EN.pdf

20. Cardoso F, Costa A, Norton L, Senkus E, Aapro M, Andre F, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast [Internet]. 2014 Oct [cited 2018 Mar 1];23(5):489-502. Available from: https://www.sciencedirect.com/science/article/pii/S0960977614001581

21. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med [Internet]. 2016 Nov 17 [cited 2018 Mar 1];375(20):1925-36. Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa1607303

22. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015 Jan;16(1):25-35.

23. Baselga J, Campone M, Piccart M, Burris HA, III, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med [Internet]. 2012 Feb 9 [cited 2018 Mar 1];366(6):520-9. Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa1109653

24. Gnant M. Overcoming endocrine resistance in breast cancer: importance of mTOR inhibition. Expert Rev Anticancer Ther. 2012 Dec;12(12):1579-89.

25. Cadoo KA, Gucalp A, Traina TA. Palbociclib: an evidence-based review of its potential in the treatment of breast cancer. Breast Cancer (Dove Med Press) [Internet]. 2014 [cited 2018 Mar 1];6:123-33. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4128689

26. Finn RS, Dering J, Conklin D, Kalous O, Cohen DJ, Desai AJ, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Res [Internet]. 2009 [cited 2018 Mar 1];11(5):R77. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2790859

27. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016 Apr;17(4):425-39.

28. Novartis Pharmaceuticals. Study to Assess the Safety and Efficacy of Ribociclib (LEE011) in Combination With Letrozole for the Treatment of Men and Pre/Postmenopausal Women With HR+ HER2- aBC. 2016 Oct 21 [cited 2018 Mar 1]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02941926 NLM Identifier: NCT02941926.

29. Novartis Pharmaceuticals. Study of Efficacy and Safety in Premenopausal Women With Hormone Receptor Positive, HER2-negative Advanced Breast Cancer (MONALEESA-7). 2014 Oct 29 [cited 2018 Mar 1]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02278120 NLM Identifier: NCT02278120.

30. Janni W, Alba E, Bachelot T, Diab S, Gil-Gil M, Beck JT, et al. Duration of response and tumor shrinkage with first-line ribociclib + letrozole in postmenopausal women with HR+, HER2- advanced breast cancer. Poster presented at: European Society for Medical Oncology Annual Meeting; 2017 Sep 8-12; Madrid (ES).

31. Blackwell KL, Paluch-Shimon S, Campone M, Conte PF, Petrakova K, Favret A, et al. Subsequent treatment for postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer who received ribociclib + letrozole vs placebo + letrozole in the phase III MONALEESA-2 study [P5-21-18] [Internet]. Poster presented at: 40th San Antonio Breast Cancer Symposium; 2017 Dec 5-9; San Antonio (TX). [cited 2017 Nov 16]. Available from: http://www.abstracts2view.com/sabcs/view.php?nu=SABCS17L_795&terms

32. Andre F, Stemmer SM, Campone M, Petrakova K, Paluch-Shimon S, Yap YS, et al. Ribociclib + letrozole for first-line treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC): Efficacy by baseline tumor markers. Cancer Res. 2017;77(13 Suppl 1):CT045.

33. O'Shaughnessy J, Petrakova K, Sonke GS, Andr F, Conte P, Arteaga CL, et al. First-line ribociclib plus letrozole in patients with de novo HR, HER2 advanced breast cancer (ABC): a subgroup analysis of the MONALEESA-2 trial. Cancer Res. 2017;4(Suppl 1).

34. Sonke GS, Hart LL, Campone M, Erdkamp F, Janni W, Verma S, et al. Ribociclib with letrozole vs letrozole alone in elderly patients with hormone receptor-positive, HER2-negative breast cancer in the randomized MONALEESA-2 trial. Breast Cancer Res Treat. 2018 Feb;167(3):659-69.

35. Yardley DA, Hart L, Favret A, Blau S, Diab S, Richards D, et al. Efficacy and safety of ribociclib plus letrozole in US patients enrolled in the MONALEESA-2 study [P5-21-27] [Internet]. Poster presented at: 40th San Antonio Breast Cancer Symposium; 2017 Dec 5-9; San Antonio (TX). [cited 2017 Nov 16]. Available from: http://www.abstracts2view.com/sabcs/view.php?nu=SABCS17L_1155&terms

36. Yap YS, Ito Y, Bornstein O, Han Y, Samant T, Liu X, et al. Phase Ib study of ribociclib (RIB) + letrozole (LET) in a subset of Asian patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) [Internet]. Abstract presented at: European Society for Medical Oncology Asia 2017 Congress; 2017 Nov 17-19; Singapore. [cited 2018 Mar 2]. Available from: http://oncologypro.esmo.org/Meeting-Resources/ESMO-Asia-2017-Congress/Phase-Ib-study-of-ribociclib-RIB-letrozole-LET-in-a-subset-of-Asian-patients-pts-with-hormone-receptor-positive-HR-human-epidermal-growth-factor-receptor-2-negative-HER2-advanced-breast-cancer-ABC-940

37. Verma S, Gil-Gil M, Hegg R, Wheatley-Price P, Kattan J, Bourgeois H, et al. Ribociclib + letrozole vs placebo + letrozole in postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC) and a high disease burden. Ann Oncol [Internet]. 2017 Apr 29 [cited 2018 Mar 2];28(Suppl 1):i7-i8. Available from: https://academic.oup.com/annonc/article/28/suppl_1/mdx137.004/3792819

38. Tolaney SM, Tan-Chiu E, Truica C, Volas-Redd G, Shtivelband M, Dalal A, et al. Quality of life and patient-reported outcomes in US patients enrolled in the MONALEESA-2 study [P1-13-12] [Internet]. Poster presented at: 40th San Antonio Breast Cancer Symposium; 2017

Dec 5-9; San Antonio (TX). [cited 2018 Mar 2]. Available from: https://www.abstracts2view.com/sabcs/view.php?nu=SABCS17L_1418&terms

39. Isaac D. Combination therapy with ribociclib improves progression-free survival in advanced breast cancer. J Clin Outcomes Manage. 2016;23(12):539-41.

40. Study report: systematic literature review and network meta-analysis of clinical trials in the first-line setting for advanced HR+ HER2- breast cancer. Boston (MA): Analysis Group, Inc; 2017 Jan.

41. Generali D, Venturini S, Rognoni C, Ciani O, Pusztai L, Loi S, et al. A network meta-analysis of everolimus plus exemestane versus chemotherapy in the first- and second-line treatment of estrogen receptor-positive metastatic breast cancer. Breast Cancer Res Treat. 2015 Jul;152(1):95-117.

42. Beck JT, Hortobagyi GN, Campone M, Lebrun F, Deleu I, Rugo HS, et al. Everolimus plus exemestane as first-line therapy in HR(+), HER2(-) advanced breast cancer in BOLERO-2. Breast Cancer Res Treat [Internet]. 2014 Feb [cited 2018 Mar 2];143(3):459-67. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3907668

43. Bergh J, Jonsson PE, Lidbrink EK, Trudeau M, Eiermann W, Brattstrom D, et al. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. J Clin Oncol. 2012 Jun 1;30(16):1919-25.

44. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. BMJ. 2013 May 14;346:f2914.

45. Matching-adjusted indirect treatment comparison report. Final: Jan 2017 data cut. New York (NY): Purple Squirrel Economics; 2017.