pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ribociclib (Kisqali) for Advanced or Metastatic Breast Cancer

June 4, 2020

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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 in combination with an aromatase inhibitor (AI) for pre- and peri-menopausal advanced or metastatic breast cancer (ABC). 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 combined with an AI for pre- and peri-menopausal ABC conducted by the Breast Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group (PAG); 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. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on ribociclib plus an AI in pre- and peri-menopausal ABC, a summary of submitted PAG Input on ribociclib plus an AI in pre- and peri-menopausal ABC, and a summary of submitted Registered Clinician Input on ribociclib plus an AI in pre- and peri-menopausal ABC, are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The reimbursement request is ribociclib (KISQALI) in combination with an AI and a luteinizing hormone-releasing (LHRH) agonist for the treatment of pre- and peri-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative ABC, as initial endocrine-based therapy (ET). The Health Canada (HC) approved indication aligns with the reimbursement request.

Ribociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signaling pathways which lead to cell cycle progression and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb).[1]

The recommended dose of ribociclib is 600 mg (3 x 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by seven days off treatment for a complete cycle of 28 days.[1] A duration of treatment is not specified. As stated in the HC product monograph, for dosing and co-administration of ribociclib with an AI, the applicable product monographs should be consulted for conditions of use.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One international, multi-centre, double-blind, randomized controlled trial (RCT) met the eligibility criteria for the systematic review. MONALEESA-7 is an ongoing, placebo-controlled, superiority trial funded by the Sponsor and conducted in 188 sites in 30 countries, including Canada (six Canadian sites; n=24).[2] A total of 672 pre- and peri-menopausal patients were randomized 1:1 to either ribociclib (n=335) or placebo (n=337) and were stratified by presence of lung or liver metastases (yes/no), prior chemotherapy for advanced disease (yes/no) and endocrine combination partner (tamoxifen/non-steroidal AI [NSAI]).

Enrolled patients had a median age of 43 years in the ribociclib group, and 45 years in the placebo group. The most common sites of metastasis were the bone (74% of patients), visceral (57%) and lymph nodes (45%). Approximately 74% of patients had an ECOG performance status of 0. Non-de novo patients made up 60% of the trial population, and of these patients, 54% had a disease-free interval of >12 months from diagnosis. Approximately 40% of patients had prior (neo)adjuvant ET, with 30% having progressed either on ET or within 12 months of stopping ET, and approximately 9% having progressed more than 12 months after ET (for 1% of patients these data were missing). Prior chemotherapy for ABC was received in 14% of trial patients.

A summary of the key outcomes from the MONALEESA-7 trial is provided in Table 1.1.

Primary Outcome – Investigator Assessed PFS

The primary outcome was investigator-assessed progression-free survival (PFS), and the primary efficacy analysis was to be performed after approximately 329 PFS events had been documented. PFS was defined as the time from randomization to either the first documented disease progression (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) or death from any cause.

As of the data cut-off date for the primary efficacy analysis (August 20, 2017), there were 318 progression events across the trial. There were fewer progression events in the ribociclib group (n=131; 39% of patients) versus the placebo group (n=187; 56% of patients) for a difference between groups that was statistically significant (hazard ratio [HR] of 0.55; 95% confidence interval [CI]: 0.44, 0.69). The median PFS was 23.8 months in the ribociclib group (95% CI: 19.2, not reached) and 13.0 months in the placebo group (95% CI: 11.0, 16.4).

With respect to subgroup analyses of the primary outcome, in general, the treatment effect remained consistent across patient subgroups, although small sample sizes in some subgroups limit interpretation of the data. The PFS treatment effect estimates for patients who received a NSAI or tamoxifen were 0.57 (95% CI: 0.44, 0.74) and 0.59 (95% CI: 0.39, 0.88), respectively. There was an indication of PFS benefit in patients who had previously progressed >12 months after the end of ET (HR of 0.75 [95% CI: 0.28, 2.02]) versus those who had progressed on or within 12 months of ET (HR of 0.59 [95% CI: 0.40, 0.87]) or those with no prior ET (HR of 0.52 [95% CI: 0.38, 0.70]); however, the small sample size in the former group (n=36) should be considered as a limiting factor when interpreting these data as it can impact the statistical power to detect differences between the subgroups. As no tests for interaction were performed and these analyses were not controlled for multiplicity, the results should be considered exploratory and interpreted accordingly.

Updated PFS data were provided by the sponsor based on the November 30, 2018 data cut-off date; at this time the median PFS was 27.5 months in the ribociclib group and 13.8 months in the placebo group (CI not reported), and the updated HR was 0.58 (95% CI: 0.48, 0.70).[3]

Table 1.1: Highlights of Key Outcomes in the MONAEESA-7 trial

OUTCOMES	MONALEESSA-7	
	Ribociclib N=335	Placebo N=337
PROGRESSION-FREE SURVIVAL - INVESTIGATOR ASSESSMENT		
*Primary efficacy analysis**		
Number of events - n (%)	131 (39)	187 (56)
-Progression	128 (38)	183 (54)
-Death[a]	3 (0.9)	4 (1)
HR (95% CI); p-value [b]	0.55 (0.44, 0.69); p<0.0001	
Median PFS, months (95% CI)	23.8 (19.2, NE)	13.0 (11.0, 16.4)
*Updated (exploratory) PFS***		
Median PFS, months (95% CI)	27.5 (Not reported)	13.8 (Not reported)
HR (95% CI) [b]	0.58 (0.48, 0.70)	
OVERALL SURVIVAL		
*1st interim analysis**		
Number of events – n (%)	43 (13)	46 (14)
*2nd interim analysis***		
Number of events – n (%)	83 (25)	109 (32)
Median OS, months (95% CI)	NE	40.9 (37.8, NE)
HR (95% CI); p-value [c]	0.71 (0.54, 0.95); p=0.00973	
OBJECTIVE RESPONSE		
*All patients**		
CR, n (%)	8 (2)	7 (2)
PR, n (%)	129 (39)	93 (28)
SD, n (%)	106 (32)	120 (36)
Non-CR/Non-PD, n (%)	60 (18)	53 (16)
PD, n (%)	24 (7)	52 (15)
Unknown, n (%)	8 (2)	12 (4)
ORR, n (%)	137 (41)	100 (30)
TIME-TO-RESPONSE		
Median time-to-response*	Not reached	Not reached
DURATION OF RESPONSE		
Median DOR, months (95% CI)	21.3 (18.3, NE)	17.5 (12.0, NE)
TIME-TO-CHEMOTHERAPY		
HR (95% CI) for receipt of chemotherapy at 42 months**	0.60 (0.46, 0.77)	
HEALTH-RELATED QUALITY OF LIFE (EORTC QLQ-C30)*		
HR (95% CI) for 10% deterioration in:		
-EORTC QLQ-C30 global health status/QOL	0.70 (0.53, 0.92)	
-EORTC QLQ-C30 physical functioning scale	0.74 (0.54, 1.01)	
-EORTC QLQ-C30 emotional functioning scale	0.72 (0.55, 0.95)	
-EORTC QLQ-BR23 breast symptoms subscale	0.68 (0.45, 1.03)	
-EORTC EQ-5D-5L, VAS scale	0.68 (0.51, 0.89)	
HARMS*		
Patients with > 0 adverse events, n (%)	329 (98)	317 (94)
Patients with > 0 serious adverse event, n (%)	60 (18)	39 (12)
Withdrawals due to adverse event, n (%)	12 (4)	10 (3)

Abbreviations: CI = confidence interval; EORTC QLQ C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; CR=complete response; DOR=duration of response; HR=hazard ratio; NE=not estimable; ORR = objective response rate; PD=progressive disease; PFS=progression-free survival; PR=partial response; SD=stable disease.

Notes:
[a] Death before progression.
[b] One-sided p-value obtained from log-rank test stratified by liver and/or lung metastases prior chemotherapy for advanced disease, and endocrine combination partner per IRT. Hazard ratio obtained from Cox PH model stratified by liver and/or lung metastases as per IRT.
[c] Log-rank test was stratified by lung and/or liver metastasis, prior chemotherapy for advanced disease, and endocrine combination partner per IRT. P-value is one-sided and was compared against a threshold of 0.00016 as determined by the Lan-DeMets (O'Brien-Fleming) alpha-spending function for an overall significance level of 0.025. Hazard ratio obtained from Cox PH model stratified by lung and/or liver metastasis, prior chemotherapy for advanced disease, and endocrine combination partner as per IRT.

Median follow-up at data cut-off dates:
*August 20, 2017: 19.2 months
**November 30, 2018: 34.6 months

Source: Tripathy 2018,[2] Im 2019,[4] FDA Clinical Review[5]

Key Secondary Outcome – Overall Survival

Overall survival (OS) was a key secondary outcome that was a part of hierarchical testing in the trial and was to be assessed at three interim analyses triggered by the total number of deaths. By the time of the pre-planned second interim analysis (total of 192 deaths, median follow-up of 34.6 months), there was a statistically significant reduction in deaths in the ribociclib group versus the placebo group; 25% (n=83) of patients in the ribociclib group and 32% (n=109) of patients in the placebo group had died (HR of 0.71 [95% CI: 0.54, 0.95], p=0.00973).[4] A pre-specified analysis of OS based on endocrine partner was performed. In patients receiving a NSAI, 25% (n=61) of patients in the ribociclib group and 32% (n=80) of patients in the placebo group had died; while in those receiving tamoxifen, results were similar with 25% (n=22) of ribociclib patients and 32% (n=29) of placebo patients with an event of death. The HR for death in those receiving a NSAI was 0.70 (95% CI: 0.50, 0.98) and for those receiving tamoxifen was 0.79 (95% CI: 0.45, 1.38).

Other Secondary Outcomes

The objective response rate (ORR) in the full or intent-to-treat (ITT) population was 41% in the ribociclib group and 30% in the placebo group. Complete responses (CR) were observed in 2% of patients in each group, while partial responses (PR) were observed in 39% of patients treated with ribociclib and 28% of patients treated with placebo. For the results of the other response outcomes assessed in the trial, refer to Table 1.1.

Health-related quality of life (HRQOL) was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30, the QLQ-BR23 (breast symptoms), and the EuroQoL 5-Dimension 5-Level Visual Analog Scale (EQ-5D-5L VAS). The primary patient-reported outcome of interest was the time-to-10% deterioration in the global health status/QOL subscale of the EORTC-QLQ-C30. A 10% deterioration in any of the scales assessed was defined as a worsening in score by 10% or more when compared to baseline, with no later improvement above this threshold during the treatment period, or death due to any cause. Most patients (99%) had completed baseline assessments, however, end of treatment assessments were only completed for a proportion of the trial population (39% of patients in the ribociclib group and 53% in the placebo group).[6] Although no formal statistical analyses were planned, the HR for time-to-deterioration in global health status/QOL was 0.70 (95% CI: 0.53, 0.92), which suggests

that overall HRQOL is not worse with ribociclib, when compared to placebo. The other scales assessed showed similar results (Table 1.1).

Harms Outcomes

The median duration of treatment exposure at the time of the primary efficacy analysis was 15.2 months in the ribociclib group and 12.0 months in the placebo group. Adverse events of any grade were reported in 98% of patients in the ribociclib group and 94% of patients in the placebo group. Grade 3 and 4 events occurred in 63% and 14% of ribociclib-treated patients, respectively, and 26% and 4% of placebo-treated patients, respectively. The most common adverse event in the ribociclib group was neutropenia; grade 3 neutropenia occurred in 51% of patients treated with ribociclib versus 3% of placebo-treated patients; and grade 4 neutropenia occurred in 10% versus 1% of patients, respectively. Febrile neutropenia occurred in 2% of patients treated with ribociclib and 1% of patients treated with placebo. QT prolongation was another notable harm, and QTcF increases of >60 msec occurred in 10% of patients in the ribociclib group compared to 2% of patients in the placebo group. Breaking this down by background ET, in the patients on tamoxifen, 16% of ribociclib patients and 7% placebo patients had increases in QTcF >60 msec, while for those on NSAI therapy, 7% of ribociclib patients versus no placebo patients experienced an increase in QTcF >60 msec. There were no cases of torsades de pointes in the trial.

Serious adverse events were reported in 18% of patients in the ribociclib group compared to 12% in the placebo group. There were no serious adverse events that occurred in more than 2% of patients in either group. Drug-induced injury was the most common serious adverse event occurring in 1.6% (n=4) of patients in the ribociclib group, and 0.4% (n=1) of patients in the placebo group, followed by dyspnea, abdominal pain, and back pain, which each occurred in 1.2% (n=3) of patients treated with ribociclib compared to 0.8% (n=2), 0%, and 0.4% (n=1) of patients treated with placebo, respectively.[7] Abdominal pain and anemia (0.8%; n=2) were the serious adverse events that occurred with ribociclib treatment but not with placebo.[7] There were two deaths in the ribociclib group that were not deemed related to the study treatment: one patient died of an intracranial hemorrhage, and one patient died of wound hemorrhage.

Withdrawals due to adverse events occurred in 4% of patients treated with ribociclib versus 3% of patients treated with placebo. The most common reason for a withdrawal due to an adverse event that was suspected to be related to drug therapy was increased alanine aminotransferase (ALT), occurring in 2% of patients in the ribociclib group and none of the patients in the placebo group.

An updated analysis of harms data based on longer follow-up showed that adverse events were consistent with those of the primary analysis.[4,7]

1.2.2 Additional Evidence

See Sections 3, 4, and 5 for a complete summary of patient advocacy group input, PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

The Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer provided input on ribociclib in combination with an AI and a LHRH agonist for treatment of pre- and peri-menopausal women with HR-positive, HER2-negative ABC, as initial ET. Both CBCN and Rethink Breast Cancer provided input based on data collected from two online surveys and two in-person interviews. Among the most commonly reported symptoms of ABC, fatigue followed by pain were rated by respondents to have the most severe impact on quality of life; furthermore, the ability to work followed by the ability to sleep were rated to be the most impacted by cancer symptoms. It was reported that the majority of patients with HR-positive ABC experienced metastases to the bones, liver, and lungs and a small fraction had metastases to the brain as well. Surgery, chemotherapy, ET, and radiation therapy were reported as current treatments for HR-positive ABC patients. Key concerns of patients included pain management, chemotherapy side effect management, treatment initiation as early as possible following diagnosis, and access to ET and targeted therapies over chemotherapy (i.e. access to many treatment options). Patients expressed a strong desire to not undergo chemotherapy, which was the likely alternative treatment option. Patient values of those with ABC included extending OS and quality of life. Regarding quality of life, patients regularly acknowledged the importance of having energy to spend time with family and friends. Overall, responses of patients with first-hand experience with the ribociclib combination under review (but not necessarily as initial endocrine-based therapy) indicated the overall tolerability of ribociclib plus an AI and LHRH agonist. Side effects were summarized to be very minimal and generally tolerable. Additionally, patient respondents of Rethink Breast Cancer's survey specific to ribociclib treatment experience unanimously recommended this therapy to other patients.

Provincial Advisory Group (PAG) Input

The PAG includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

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

Clinical factors:

- Clarity on eligible patient population

Economic factors:

- Additional healthcare resources for monitoring and management of adverse events

Registered Clinician Input

One joint input submission from two clinicians on behalf of Cancer Care Ontario (CCO) provided input on the use of ribociclib in combination with an AI and a LHRH agonist for the treatment of pre- and peri- menopausal women with HR-positive, HER2-negative ABC as initial ET. Based on the results of the MONALEESA-7 trial, the clinicians noted that the ribociclib combination with an AI and a LHRH agonist is superior to ET alone and exhibits an acceptable toxicity profile; thus, the CCO clinicians expect the treatment combination to be widely used in clinical practice.

Despite availability of other ET options for pre- and peri- menopausal women with HR-positive, HER2-negative ABC, the CCO clinicians indicated they would administer the ribociclib combination in the first-line setting over abemaciclib, palbociclib, and ribociclib plus fulvestrant based on the clinical trial evidence. The CCO clinicians felt that there is limited evidence to extend the use of ribociclib plus an AI to HER2-positive patients but would consider administering ribociclib plus an AI and LHRH agonist in male breast cancer patients. Selection of the appropriate therapy would depend on the availability of everolimus, prior treatment with ET, and clinical features that may suggest the preferability of chemotherapy. Contraindications were reported as per the ribociclib product monograph; namely, ribociclib is contraindicated in patients with hypersensitivity to the drug or composite ingredients in the formulation and in patients with or at risk of pathological prolongation of the QT interval.

Summary of Supplemental Questions

Supplemental issues relevant to the pCODR review and to the PAG were identified while developing the review protocol and are outlined in section 7:

- Summary and Critical Appraisal of a Sponsor-submitted Indirect Treatment Comparison (ITC)

Since the MONALEESA-7 trial did not include a comparison to an active relevant treatment comparator, the sponsor conducted an ITC to estimate the relative efficacy (PFS) and safety of ribociclib plus a NSAI versus selected treatments for pre- and peri-menopausal women with HR-positive, HER2-negative ABC who have not received prior ET for ABC. The ITC was used to inform the pharmacoeconomic model supporting the reimbursement request.

Eligible trials were identified from a systematic review of electronic databases performed in April 2018 seeking RCTs and was supplemented with studies identified through a more targeted review of the literature. The ITC of PFS was conducted using the Bucher method, while adverse events were evaluated using an unanchored (naïve) comparison. After a request from pCODR, the ITC was updated to include other CDK 4/6 inhibitors combined with AI or fulvestrant as relevant comparators. The ITC uses the most recent data cut-off date for PFS from the MONALEESA-7 trial, which was November 30, 2018.

The ITC included nine trials; however, there were no trials of CDK 4/6 inhibitors whose populations mirrored that of the MONALEESA-7 trial, thus limiting the conclusions that can be drawn from the analysis. The only available comparisons were based on patient subgroup data, and these suggested no clear differences in efficacy between ribociclib and other CDK 4/6 inhibitors in this population. The ITC results showed that there was improved efficacy for ribociclib combined with a NSAI when compared with palbociclib plus fulvestrant (HR of 0.69; 95% CI: 0.37, 1.29) or abemaciclib plus fulvestrant (HR of 0.57; 95% CI: 0.31, 1.04); however, these differences were not statistically significant. The pCODR Methods Team considered the significant heterogeneity in patient populations among the included trials as a major limitation of the ITC; there were notable differences across the trials related to menopausal status, endocrine partner, disease-free interval, inclusion of de novo ABC patients, and line of therapy, as well as missing information on other important patient and trial characteristics (i.e., patient demographics, study locations, PFS definitions and assessment schedule, median follow-up time). Overall, the ITC results should be interpreted with caution given the significant clinical heterogeneity across trials that could impact their comparability to the MONALEESA-7 trial and produce biased estimates of relative treatment effect.

Comparison with Other Literature

No comparisons to other literature were identified.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence from the MONALEESA-7 trial; an assessment of the trial limitations and potential sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 1.2: Assessment of generalizability of evidence from the MONALEESA-7 trial

Domain	Factor	Evidence: MONALEESA-7[2]	Generalizability Question	CGP Assessment of Generalizability
Population	Age	The mean age of women in the trial was 43 years (range, 25-58 years)	Do the trial results apply to all adult patients?	Yes. A recent pooled analysis of CDK 4/6 trials in HR-positive, HER2-negative ABC suggests similar clinical benefit across all age groups of patients, including those over the age of 75.[8]
	Performance status	% of patients in the trial with: ECOG of 0: 75% ECOG of 1: 24% Patients with an ECOG of 2 were excluded from the trial.	Are the trial results applicable to patients with an ECOG performance status of 2 or greater?	All randomized trials of CDK 4/6 inhibition in HR-positive, HER2-negative ABC have excluded patients with a PS of 2 or greater; therefore, generalizability cannot be assumed. As most patients in clinical practice will have a PS of 0 or 1, the CGP felt the use of ribociclib should be limited to patients with an ECOG PS ≤1.
	Disease-free interval	% of patients in the trial with: Newly diagnosed, de novo disease: 40% Non-de novo disease: 60% Disease-free interval of ≤ 12 months from diagnosis: 6% Disease-free interval of >12 months from diagnosis: 54%	Is the proportion of de novo disease reflective of the Canadian patient population AND are trial results applicable to this patient population?	The de novo disease status rate in the trial is not reflective of the general Canadian population as Canadian population rates are much lower, generally estimated at ≤ 5%. The trial subgroup analysis by disease-free interval after diagnosis demonstrated a consistent treatment effect across de novo and non-de novo patients, in patients with a disease-free interval of >12 months but not for patients with a disease-free interval ≤ 12 months. The result in this latter subgroup was likely too small to reliably estimate a treatment effect and the CGP would still consider this group of patients for

Domain	Factor	Evidence: MONALEESA-7[2]	Generalizability Question	CGP Assessment of Generalizability
				treatment with ribociclib.
	CNS metastases	Patients with CNS metastases were excluded from the trial.	Are the trial results applicable to patients with CNS metastases?	Very limited data exist on the role of CDK 4/6 inhibitors for patients with brain metastases. Although these patients have been excluded from all randomized phase 3 trials, extrapolation of clinical benefit would be reasonable to assume in the setting of treated/asymptomatic brain metastases. However, CNS-specific benefit is unknown and should not be assumed.
	Gender	All patients in the trial were female.	Do the trial results apply to male patients with advanced or metastatic breast cancer?	As per all clinical trials for ABC, data on male gender is extremely limited. Potential clinical benefit for male patients is usually extrapolated from the data for female patients and is reasonable for this indication.
	Inflammatory breast cancer	Patients with inflammatory breast cancer were excluded from the trial.	Are the trial results generalizable to patients with inflammatory breast cancer?	Almost all cases of inflammatory breast cancer are treated with curative intent neoadjuvant chemotherapy and were excluded from all CDK 4/6 clinical trials in ABC. Therefore, it is clinically appropriate to follow the trial design and not generalize the evidence to patients with primary inflammatory breast cancer.
Intervention	Ribociclib combined with NSAI (and LHRH agonist)	Ribociclib combined with either a NSAI (letrozole/anastrozole or tamoxifen (and LHRH agonist)	Is ribociclib the only CDK4/6 inhibitor that can be used with an AI and ovarian suppression in the pre/perimenopausal patient population?	The MONALEESA-7 trial is the only trial of CDK 4/6 inhibitors in ABC specifically focused to pre-/peri-menopausal patients. The trial mandated ovarian suppression thus rendering all included patients biochemically and clinically post-menopausal. All other randomized trials of CDK 4/6 inhibitors limited

Domain	Factor	Evidence: MONALEESA-7[2]	Generalizability Question	CGP Assessment of Generalizability
				accrual to post-menopausal patients. It is reasonable to assume that clinical benefit would be similar across CDK 4/6 therapies for pre-/peri-menopausal females regardless of mechanism of menopausal induction (i.e., natural, surgical, radiation-induced, LHRH analogue-induced). Clinicians may choose to switch CDK4/6 inhibitor if patients show intolerance. Either NSAI used in the trial can be used in combination with ribociclib. Although a treatment option in this trial, tamoxifen is not a recommended ET partner with ribociclib due to additive effects on QT prolongation.
	Prior Therapy	% of patients in the trial with: No prior (neo)adjuvant ET: 60% Progression on or within 12 months of the end of ET: 30% Progression >12 months after the end of ET: 9% Prior chemotherapy for advanced disease: 14%	Are the trial results generalizable to patients with prior exposure to ET, chemotherapy or CDK 4/6 inhibitor-based therapy in the advanced/metastatic setting?	Patients with prior exposure to ET or CDK 4/6 inhibitor-based therapy in the advanced/metastatic setting were excluded from MONALEESA-7; thus, the available evidence does not support the use of a CDK 4/6 inhibitor plus ET following disease progression on a different CDK 4/6 inhibitor in this setting as all RCTs have excluded patients with prior CDK 4/6 exposure. For patients with disease progression on ET alone in this setting, use of a CDK 4/6 inhibitor in conjunction with ET is reasonable based on the totality of evidence supporting the role of CDK 4/6 inhibitors as second-line therapy.
Comparator	Standard of Care Matched Placebo	The comparator in the trial was a matched placebo with either a NSAI or tamoxifen, and a LHRH agonist.	Are the results of the ITC generalizable to patients who may receive these	Refer to section 1.1.2 for the CGP's interpretation of the ITC results.

Domain	Factor	Evidence: MONALEESA-7[2]	Generalizability Question	CGP Assessment of Generalizability
		The CGP identified these additional treatments as relevant comparators: • Palbociclib + AI • Abemaciclib + AI • Palbociclib + fulvestrant • Abemaciclib + fulvestrant The sponsor provided an ITC that included indirect comparisons of ribociclib plus a NSAI to these relevant comparators. Please refer to section 7 for more information.	relevant comparators?	

Abbreviations: ABC=advanced or metastatic breast cancer; AI=aromatase inhibitor; CDK=cyclin-dependant kinase; CGP=Clinical Guidance Panel; CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; ET=endocrine therapy; HER2= human epidermal growth factor receptor 2; HR=hormone receptor; ITC=indirect treatment comparison; LHRH=luteinizing hormone-releasing hormone; NSAI=non-steroidal aromatase inhibitor.

1.2.4 Interpretation

Burden of Illness

In 2019, it was estimated that 26,900 Canadian women would be diagnosed with breast cancer with 5,000 deaths expected due to metastatic disease.[9] In Canadian women, breast cancer accounts for approximately 25% of all cancer incidence cases and 13% of all cancer deaths with 1 in 33 women dying of metastatic disease over the course of their lifetime.[9]

Roughly 70-80% of breast cancers are potentially endocrine sensitive and HER2-negative as determined by an analysis of estrogen and/or progesterone receptors (HR-positive) and HER2 expression or gene amplification in the primary tumour and/or in biopsies from a metastatic site of disease. The vast majority of these patients will be offered adjuvant endocrine therapy following curative-intent surgery, either with or without antecedent chemotherapy.

In general, adjuvant ET consists of a single agent AI for reliably post-menopausal patients or tamoxifen for pre- and peri-menopausal patients. For some pre-menopausal patients with high-risk disease and persistent menses despite adjuvant chemotherapy, ovarian suppression with an LHRH analogue will be recommended in conjunction with either tamoxifen or an AI.

Most women developing HR-positive, HER2-negative metastatic disease are candidates for single-agent ET with non-curative intent. Classically, this treatment option was most often recommended for those patients with relatively limited disease burden to non-life threatening sites such as bone and/or soft tissue, as well as for some with small volume visceral disease who were not experiencing rapidly progressing or significantly symptomatic disease, and particularly for those with a long disease-free interval (e.g. > 2 years) since completion of adjuvant ET. Usual first-line therapy included tamoxifen for pre- and peri-menopausal women and an AI for post-menopausal women.

Need

All previous RCTs evaluating a CDK 4/6 inhibitor as first-line treatment have included women who were post-menopausal at the time of development of metastatic disease. The MONALEESA-7 trial is the only trial that has included pre- and peri-menopausal patients as part of eligibility criteria for enrollment.[2] Although pre- and peri-menopausal at trial inclusion, all patients were treated with an effective LHRH analogue, thereby rendering all patients biochemically post-menopausal and then eligible for therapy with ribociclib plus endocrine therapy (either AI or tamoxifen). At present, CDK 4/6 inhibitors (ribociclib, palbociclib, and abemaciclib) are only approved for post-menopausal women with the totality of evidence suggesting significant clinical benefit and excellent tolerance in general compared to single agent AI (Table 1.3). The exclusion of pre-menopausal women in all prior RCTs has resulted in an important unmet clinical need for this patient population as first-line treatment options were limited to single-agent ET +/- ovarian suppression or cytotoxic chemotherapy.

Table 1.3: CDK4/6 inhibitors in ABC: first-line trials

Trial	Regimen	Phase	N	Menopausal Status	ORR*, %	PFS, Months	HR	95% CI
PALOMA-1	Letrozole ± palbociclib	2	165	Post	39 vs 55	10.2 vs 20.2	0.49	0.22-0.75
PALOMA-2	Letrozole ± Palbociclib	3	666	Post	44 vs 55	14.5 vs 24.8	0.58	0.46-0.72
MOLALEESA-2	Letrozole ± ribociclib	3	668	Post	39 vs 55	16.0 vs 25.3	0.57	0.46-0.70
MONARCH-3	NSAI ± abemaciclib	3	493	Post	46 vs 61	14.8 vs 28.2	0.54	0.42-0.70
MONALEESA-7	ET + OS ± ribociclib	3	672	Pre-/Peri-	36 vs 51	13.0 vs 23.8	0.55	0.44-0.69
MONALEESA-3	Fulvestrant ± ribociclib	3	367	Post	36 vs 51	18.3 vs NR	0.58	0.42-8.80

*Patients with measurable disease

Patient input for this submission was supplied by CBCN and Rethink Breast Cancer, and included information obtained from two online patient surveys, as well as nine patients who had experience with the treatment under consideration with of them fully matching the reimbursement request. Six of the nine patients with first-hand experience of ribociclib plus a NSAI were interviewed and all attested to the tolerability of the combination as well as treatment efficacy, with all indicating that they would recommend it to other patients. These patients voiced a strong desire to avoid or delay undergoing chemotherapy, which was the likely alternative treatment option.

Effectiveness

MONALEESA-7 is an international, multi-centre, randomized, double-blind, placebo-controlled phase 3 trial comparing ribociclib to placebo in addition to ET with ovarian suppression and either a NSAI or tamoxifen in 672 pre- and peri-menopausal women with HR-positive and HER2-negative incurable breast cancer.[2] Patients were aged 18-59 years with an ECOG performance status of 0-1. ET and chemotherapy received in the adjuvant or neoadjuvant setting was permitted, as was up to one line of chemotherapy for advanced disease. The primary outcome of the trial was investigator-assessed PFS.

At the primary efficacy analysis, which was performed after a median follow-up time of 19.2 months, the median PFS was 23.8 months (95% CI: 19.2, not reached) in the ribociclib group compared with 13.0 months (95% CI: 11.0, 16.4) in the placebo group (HR of 0.55; 95% CI: 0·44, 0.69; p<0.0001).

An updated (exploratory) analysis of PFS based on the November 30, 2018 data cut-off date was provided by the sponsor based on a median follow-up time of 34.6 months and showed consistent results to the primary analysis; the median PFS was 27.5 months with ribociclib and 13.8 months with placebo (CI not provided) and the updated HR was 0.58 (95% CI: 0.40, 0.70).[3]

The protocol-specified second interim analysis of OS demonstrated a significantly longer OS with ribociclib plus a NSAI compared to ET alone; the estimated OS at 42 months of follow-up was 70.2% (95% CI: 63.5, 76.0) in the ribociclib group and 46.0% (95% CI: 32.0, 58.9) in the placebo group (HR of 0.71; 95% CI, 0.54, 0.95; p = 0.00973).[4] The survival benefit observed in the subgroup of patients who received a NSAI was consistent with that in the overall population (HR of 0.70; 95% CI: 0.50, 0.98).[4]

An exploratory analysis of the outcomes of patients who moved onto subsequent therapy after disease progression (PFS2) revealed similar exposure to post-progression therapies between the two groups with approximately 69% of patients in the ribociclib group and 73% of patients in the placebo group receiving post-progression therapies.[4] Chemotherapy alone (22% versus 29%, respectively) and ET alone (22% and 20%, respectively) were the most common first subsequent antineoplastic therapies.[4] This highlights that significant differences in the use of post-progression treatments are unlikely to have impacted the observed OS benefit reported.The time from randomization to disease progression during receipt of second-line therapy or to death was longer in the ribociclib group than in the placebo group (HR of 0.69; 95% CI: 0.55, 0.87), with fewer PFS2 events in the ribociclib group (38% versus 48%, respectively).[4]

Patient-reported HRQOL was evaluated as an exploratory outcome of MONALEESA-7 with the primary patient-reported outcome of interest being the time-to-10% deterioration in the global health status subscale of the EORTC-QLQ-C30. A definitive 10% deterioration was defined as a worsening in score by 10% or more when compared to baseline, with no later improvement above this threshold during the treatment period, or death due to any cause. No formal statistical analyses were performed for HRQOL outcomes. Most patients (99%) completed baseline assessments, however, end of treatment assessments were completed for a proportion of trial patients (39% of patients in the ribociclib group and 53% in the placebo group).[6] It should be noted that the amount of missing data introduces the potential for bias in the assessment of HRQOL since remaining patients could inherently be different when compared to patients who were lost to follow-up (i.e., more likely to exhibit improved HRQOL, as they are more likely to be responders and less likely to be experiencing adverse effects from study treatment). The results showed that time-to-10% definitive deterioration of global health status favoured ribociclib with a median time-to-deterioration that was not reached in the ribociclib group versus 21.2 months in the placebo group (HR of 0.70; 95% CI: 0.53, 0.92). Other subscales (emotional functioning; EQ-5D-5L VAS) also appeared to favour ribociclib while others indicated no difference between treatment groups (physical functioning, breast symptoms).

Safety

The grade 3 or 4 adverse events reported in more than 10% of patients in either treatment group were neutropenia (61% of patients in the ribociclib group and 4% of patients in the placebo group) and leucopenia (14% and 1%, respectively). Serious adverse events occurred in 18% of patients in the ribociclib group and 12% of patients in the placebo group. Of these events, 4% in the ribociclib group and 2% in the placebo group were attributed to the study treatment with treatment discontinued due to adverse events in 4% and 3% of patients in the ribociclib and placebo groups, respectively. A total of 11 deaths occurred (five [1%] in the ribociclib group and six [2%] in the placebo group) during or within 30 days after treatment. Most deaths in both groups were due to progression of the underlying

disease (three [1%] in the ribociclib group and six [2%] in the placebo group) and none were deemed related study treatment.

Dose interruptions or reductions owing to an adverse event of QTcF interval prolongation occurred in 13 (4%) of 335 patients in the ribociclib group and three (1%) of 337 patients in the placebo group. None of the patients with a QTcF prolongation event had clinical symptoms or arrhythmias and there were no cases of torsades de pointes. Although tamoxifen was included as an ET option in the trial, it is not a recommended ET partner to ribociclib due to additive effects on QTcF prolongation. In the trial, QTcF increases of >60 msec occurred in 10% of patients treated with ribociclib compared to 2% of patients treated with placebo. In patients on tamoxifen, 16% (n=14) on ribociclib and 7% (n=6) on placebo had increases in QTcF >60 msec, while for patients on a NSAI, 7% (N=18) on ribociclib compared to 0% on placebo experienced an increase in QTcF >60 msec. Based on these safety findings, HC did not include tamoxifen in combination with ribociclib as part of the approved HC indication and therefore it is not included in the request for reimbursement.

Ribociclib requires more extensive safety assessments (electrocardiograms [ECG]s, Liver function tests) compared to other CDK 4/6 inhibitors, particularly in the first couple of months of therapy as the drug reaches steady-state. Patients becoming ill due to an unrelated disease such as a gastroenteritis while on treatment with ribociclib should have electrolytes closely monitored and replaced if needed.

Adverse events observed in the two treatment groups after longer follow-up (assessed at the second interim analysis of OS) remained consistent with those seen at the primary analysis. Key grade 3 or 4 adverse events of special interest were neutropenia (in 63.5% of patients in the ribociclib group and 4.5% in the placebo group), febrile neutropenia (in 2% and 1% of patients, respectively), hepatobiliary toxic effects (in 11% and 6.8%, respectively), and prolonged QT interval (in 1.8% and 1.2%, respectively).

Other Considerations

The PAG raised several points to be considered if ribociclib combined with a NSAI were to be recommended for reimbursement, specifically with respect to the choice of CDK 4/6 inhibitor, the eligible patient population, sequencing of treatments, and generalizability of evidence. For the CGP's assessment on issues related to generalizability of the evidence, refer to Table 1.2 in section 1 of this report. The CGP has addressed the other points below:

- Although not specifically investigated, the possible addition of ribociclib for a pre-menopausal woman currently on an AI (and ovarian suppression) whose disease has not progressed could be considered.
- Switching to a different CDK 4/6 inhibitor (ribociclib with abemaciclib or palbociclib) for the respective indications, if a patient is intolerant to one is reasonable and likely will depend on the cause of intolerance.
- If a patient has oligoprogression and is deriving clinical benefit overall in the judgement of the treating clinician, continuing treatment with ribociclib plus an AI would be reasonable.
- In regard to PAG's questions about the appropriate sequencing of all available treatments; specifically:
    - Whether there is a preference for a specific CDK 4/6 inhibitor (e.g., ribociclib, abemaciclib, or palbociclib) and if they can considered therapeutically equivalent:

the sponsor provided an ITC (refer to Section 7) to estimate the relative treatment effects of CDK 4/6 inhibitor combinations but a critical appraisal of this analysis indicated the results should be interpreted with caution due to the heterogeneity in patient populations across the included trials that could impact their comparability to the MONALEESA-7 trial. While most clinicians consider CDK 4/6 inhibitors therapeutically equivalent in terms of efficacy, there are notable differences in required monitoring and supportive care considerations that may make one agent preferable to the others for individual patients. Palbociclib requires no routine ECG or liver function test monitoring like ribociclib, and abemaciclib can be complicated by dose-limiting diarrhea which must be aggressively managed.

- Preference for ribociclib plus an AI or ribociclib plus fulvestrant in the endocrine-naïve/sensitive ABC setting: access to fulvestrant has been problematic across Canada although the introduction of a generic formulation may expand availability. Ribociclib plus AI or fulvestrant has demonstrated clinical benefit in this patient population and clinical treatment decisions may depend partly on access to fulvestrant as well as on other factors such as patient preference or line of therapy.
- Treatments patients can receive following disease progression on ribociclib plus an AI: treatment options after disease progression on ribociclib plus an AI can include rotation to a different single agent AI (non-steroidal to steroidal AI), tamoxifen, fulvestrant (if available), everolimus plus exemestane, or single agent/combination cytotoxic chemotherapy, as well as clinical trial options depending on availability. In MONALEESA-7, post-progression receipt of a CDK 4/6 inhibitor was 10% in the ribociclib group versus 19% in the placebo group; however, outcome data are unavailable regarding the clinical benefit of post-progression CDK 4/6 treatment.
- Whether there is evidence to support re-treatment with ribociclib or another CDK 4/6 inhibitor in patients whose disease progressed on or after ribociclib: there is no evidence supporting re-treatment with a CDK 4/6 inhibitor in the setting of disease progression on a CDK 4/6 inhibitor.
- Sequencing of everolimus plus exemestane: everolimus and exemestane remains a treatment option for this patient population after disease progression on a CDK 4/6 inhibitor; however, it is unclear as to whether the clinical benefit of this combination is maintained in the context of prior CDK 4/6 exposure. Due to the robust nature of the clinical data supporting CDK 4/6 inhibitors as first-line therapy, as well as the fact that the majority of patients in the BOLERO-2 RCT supporting everolimus and exemestane were treated in the second-line setting, the CGP believes most clinicians would favour sequencing everolimus and everolimus after a CDK 4/6 inhibitor combination.

1.3 Conclusions

- The CGP concluded that there is a net overall clinical benefit of ribociclib in combination with a NSAI (plus ovarian suppression) for pre- and peri-menopausal women with HR-positive, HER2-negative incurable ABC based on the strength of one high-quality randomized, double-blind, placebo-controlled phase 3 trial, which demonstrated a clinically meaningful prolongation in PFS and OS, an acceptable safety profile, and no apparent detriment on HRQOL.
- The safety analysis of ribociclib plus a NSAI did not reveal unexpected toxicities in this patient population. Although tamoxifen was included as an ET treatment partner to

ribociclib in the MONALEESA-7 trial, it is not a recommended ET partner due to additive effects on QTcF prolongation.

- Access to appropriate ovarian suppressive therapy must be available for pre-menopausal patients to meet treatment eligibility requirements (as per the MONALEESA 7 trial). This includes monthly LHRH analogue, therapeutic oophorectomy and/or ovarian irradiation.

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 is the most common diagnosed malignancy in Canadian women, with an estimated 26,900 new cases and 5,000 deaths in 2019.[9] While many women diagnosed with early stage breast cancer will be cured with treatment, all will continue to have some risk of developing metastatic disease despite multimodality adjuvant therapy (e.g., chemotherapy, ET, radiation and targeted therapy). It is also estimated that, in Canada, approximately 5-10% of women present with de novo metastatic breast cancer. ABC remains incurable and is treated systemically with palliative intent with a median life expectancy of approximately 2-3 years.[10]

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. Several systemic treatment options are available and the selection and sequencing of these are dependent on several factors including the biological characteristics of the breast cancer (ER, PR, and HER-2 receptor status), overall clinical condition and comorbidities, performance (functional) status, pace of disease progression, degree of impending threat to life, need for symptom control and patient preferences. Systemic options broadly include ET, 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.[11] In the absence of rapidly progressive disease or visceral crisis, ET is usually considered first-line palliative treatment in HR-positive, HER2 negative disease, based on its efficacy and favorable toxicity profile. Commonly used options include selective estrogen receptor modulators (e.g. tamoxifen), AI (e.g. anastrozole, letrozole, and exemestane), selective estrogen receptor degraders (e.g. fulvestrant), and less commonly, progesterone agents (e.g. megestrol acetate). AI and fulvestrant are only appropriate for post-menopausal patients whereas tamoxifen is effective regardless of menopausal state. Ovarian suppression with LHRH agonists may also be employed in conjunction with systemic ET for pre-menopausal women. Unfortunately, all endocrine-sensitive breast cancers inevitably develop acquired resistance to ET, necessitating a change in systemic treatment. Additionally, a small proportion of patients with HR-positive disease at initial presentation do not respond to first-line ET, and are considered to have primary endocrine resistance. Much research has focused on the understanding of intracellular pathways and mechanisms involved with both acquired and primary resistance in order to optimize disease control for endocrine-sensitive disease, particularly in light of the favourable toxicity profiles of endocrine-based therapies as compared to cytotoxic chemotherapy. Recent pre-clinical and clinical investigation has resulted in the development and clinical utilization of a number of molecularly targeted agents for this patient population including mTOR signaling pathway and CDK4/6 inhibitors.

For pre-menopausal patients, endocrine therapeutic options are somewhat more limited in the absence of ovarian suppression or ablation rendering them post-menopausal as standard options such as AI, fulvestrant and, until recently CDK 4/6 inhibitors, are only indicated for post-menopausal women.

2.2 Accepted Clinical Practice

Currently, there is no standard approach for the management of HR-positive ABC with the sequencing of endocrine agents in the metastatic setting remaining a topic of intense investigation. Treatment approaches often consider 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, metastatic burden, location of disease sites as well as degree of impending threat to health and/or life, clinical status and co-morbidities, individual preferences, and provincial treatment funding.

Recent developments of therapeutic agents have resulted from pre-clinical investigation of resistance mechanisms to ET. One such mechanism involves constituent activation of the PI3K-Akt-mTOR signaling pathway.[12] Targeted agents such everolimus have been developed to block this signal transduction pathway, and have demonstrated an impact on PFS in combination with exemestane (AI) versus exemestane alone following disease progression on a NSAI.[13] Another signaling pathway involves aberrant dysregulation of the cell division cycle. Cellular replication involves a host of tightly regulated steps coordinated by specialized cell cycle signaling molecules, such as CDK. CDK are a series of small molecule serine threonine kinase enzymes that combine with their associated cyclins to regulate the passage of cells through growth and division cycles. Studies have discovered multiple genetic mutations which activate these pathways, leading to uncontrolled growth and rapid division of malignant cells. Inhibitors of CDK activity have resulted in an additional therapeutic pathway impacting the progression of metastatic HR-positive breast cancer.

Ribociclib (KISQALI, Novartis), palbociclib (IBRANCE, Pfizer) and abemaciclib (VERZENIO, Lilly) are reversible, oral, small molecule inhibitors of CDK 4 and 6 which stop progression through the cell cycle when partnered with cyclin D. CDK 4/6 and cyclin D play a crucial role in the regulation of the G1/S transition of the cell cycle through regulation of the phosphorylation of pRB (retinoblastoma protein). A number of pre-clinical and clinical studies have demonstrated that the combination of ribociclib, palbociclib or abemaciclib with ET (including tamoxifen, AI, or fulvestrant) are able to overcome endocrine resistance, and improve PFS, and in some studies, OS. In addition, the combination has been found to have a generally excellent safety profile, especially when compared with standard chemotherapy. Reversible myelosuppression without myeloid toxicity results in uncomplicated neutropenia being the most common adverse event but episodes of febrile neutropenia are very rare.[14-19]

Ribociclib is an orally administered, selective small molecule inhibitor of CDK 4/6 administered on a three-week daily schedule followed by one-week rest. The dosing involves three 200 mg tablets taken once daily with dose adjustments for toxicities in 200 mg increments.

Idiosyncratic toxicities can include prolongation of the QT interval as well as hepatic transaminitis, both of which arise in approximately 5-7% of patients and for which there are both ECG and serum chemistry monitoring recommendations.

Earlier studies have demonstrated both tolerability and clinical benefit, and ribociclib has now been investigated in three large RCT:

- MONALEESA 2: ribociclib plus letrozole versus placebo plus letrozole
- MONALEESA 3: ribociclib plus fulvestrant versus placebo plus fulvestrant
- MONALEESA 7: ribociclib plus NSAI/tamoxifen plus goserelin versus placebo plus NSAI/tamoxifen plus goserelin

2.3 Evidence-Based Considerations for a Funding Population

The evidence-based population suitable for consideration of ribociclib in combination with a NSAI for the treatment of HR-positive, HER2-negative ABC would be the same population included in the MONALEESA 7 trial. This includes women with incurable HR-positive, HER2-negative locally advanced or metastatic breast cancer at any time point after curative-intent treatment or presenting with de novo incurable disease who are pre- or peri-menopausal between the ages of 18-59. Eligible patients could have received up to one line of chemotherapy for ABC but no prior lines of ET. Patients would need to have adequate performance status (ECOG performance status of 0-1) as well as adequate organ and bone marrow function.

MONALEESA 7 excluded patients who received any ET for ABC. Whether the clinical benefit of ribociclib plus a NSAI plus goserelin would extend to a more heavily pre-treated patient population is unknown.

2.4 Other Patient Populations in Whom the Drug May Be Used

Due to the observed effect of ribociclib on QTc/QTcF intervals, patients with a baseline ECG demonstrating a QTc/QTcF interval of > 450 msec are not candidates for ribociclib-based therapy as per the inclusion criteria of all MONALEESA studies investigating ribociclib.

There are no data available to address the patient population with uncontrolled, untreated cerebral metastases and these patients are not candidates for ribociclib-based therapy in the absence of CNS disease control. MONALEESA 7 excluded patients with any CNS disease although it would be reasonable to consider the use of ribociclib-based therapy for patients with controlled/asymptomatic brain metastases whom otherwise meet criteria for treatment.

Although the clinical trial initiated concurrent ovarian suppression with NSAI and ribociclib, there may be situations within the Canadian context where patients are treated with ovarian suppression and NSAI alone. In these situations, it would be reasonable to consider the addition of ribociclib to ongoing treatment as long as all other criteria are met for ribociclib consideration. It is unknown if ribociclib should be added at time of progression or in the context of ongoing stable disease.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer provided input on ribociclib (KISQALI) in combination with an AI and a LHRH agonist for treatment of pre- or peri-menopausal women with HR-positive, HER2-negative ABC, as initial ET. A summary of the data gathered by the CBCN and Rethink Breast Cancer is found in Table 3.1.

The CBCN provided input based on data collected from two online surveys with scoring options and free form commentary, two in-person interviews, and a review of current studies and grey literature. The more recent survey titled "CBCN's 2017 Survey of Metastatic Breast Cancer Patients" collected data from 180 Canadian MBC patients who were contacted through CBCN's patient network, website, and social media. Notably, 65 respondents of the 2017 survey had HR-positive breast cancer and 42 of them were also HER2-negative (HR-positive, HER2-negative breast cancer patients) but none of the patients disclosed whether they were treated with ribociclib. The earlier survey titled "CBCN's 2012 Metastatic Breast Cancer Patient and Caregiver Survey Report" was conducted in collaboration with Rethink Breast Cancer and collected data from 71 patient and 16 caregiver respondents who were contacted through membership databases of the CBCN and other patient organizations. None of the patient respondents of CBCN's 2012 survey had experience with the treatment under review. Additionally, the CBCN interviewed two Canadian patients with experience with the treatment under review; however, the second patient was previously treated with surgery, radiation, and zoladex (goserelin).

Rethink Breast Cancer provided input based on data collected from two online patient surveys. Both surveys were advertised through mailing lists of Rethink Breast Cancer, Young Women's Network, and other partner organizations; postings on social media (Facebook and Twitter); and online discussion boards (the Breastcancer.org, Cancer Connection, and Cancer Survivors Network). A general survey of ABC patients asked about the impact of ABC on patients and the effect of current treatments. The survey was conducted between August 2nd, 2018 and November 27th, 2018 and a total of 74 women completed the survey. Of these respondents, 60 were from Canada with representation of Alberta, British Columbia (BC), New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Quebec, and Saskatchewan; nine were from the United States (US); and there was one respondent each from Guyana, India, Ireland, New Zealand, and the United Kingdom (UK). Of the 74 respondents, five were diagnosed in 2018; 11 were diagnosed in 2017; nine were diagnosed in 2016 and 2014; six were diagnosed in 2015, 2013 and 2012; and 22 were diagnosed earlier. A second survey regarding experience with ribociclib treatment for HR-positive, HER2-negative advanced or metastatic breast cancer was conducted between August 13th and 31st, 2019. Of the 26 women respondents, 13 were from Canada with representation of Alberta, BC, Ontario, Quebec, and Saskatchewan; six were from Australia; five were from the US; and two were from the UK. Among the 26 respondents, 17 were pre-menopausal; of these pre-menopausal women, all were treated with ribociclib with an AI, nine were treated with ribociclib in combination with an AI and LHRH agonist, and nine received ribociclib as initial endocrine therapy. Of note, Rethink Breast Cancer did not ask about any other ribociclib combinations.

Among the common symptoms of advanced and metastatic breast cancer cited by respondents, fatigue followed by pain were rated to have the most severe impact on quality of life; furthermore, the ability to work followed by the ability to sleep were rated to be the most impacted by cancer symptoms. It was reported that the majority of patients with HR-positive ABC experienced metastases to the bones, liver, and lungs and a small fraction had metastases to the brain as well. Additionally, surgery, chemotherapy, hormone therapy, and radiation therapy were reported as current treatments for HR-positive ABC patients. Namely, the Rethink Breast Cancer survey reported letrozole (Femara) to be the most commonly administered treatment as 22 out of 26 HR-positive, HER2-negative breast cancer patients indicated having experience with this drug. Key concerns of HR-positive breast cancer patients included pain management, chemotherapy side effect management, treatment initiation as early as possible following diagnosis, and access to

hormone therapy and targeted therapies over chemotherapy (i.e. access to many treatment options). Patients expressed a strong desire to not undergo chemotherapy, which was the likely alternative. Patient values of those with ABC included extending overall survival (OS) and quality of life. The CBCN noted that the value of extending OS to patients cannot be overestimated. Patients living with ABC are aware that symptoms will worsen until death; thus, they embrace opportunities to try new treatments with demonstrated efficacy. Quality of life was also noted to be very important; patients regularly acknowledge the importance of having energy to spend time with family and friends. Overall, responses of patients with first-hand experience with the ribociclib combination under review (but not necessarily as initial endocrine-based therapy) indicated the overall tolerability of ribociclib plus an AI and LHRH agonist. Side effects were summarized to be very minimal and generally tolerable. Additionally, patient respondents of Rethink Breast Cancer's survey specific to ribociclib treatment experience unanimously recommended this therapy to other patients.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient advocacy groups.

Table 3.1 Summary of the information gathered by the patient groups

Patient Group	Information Gathering Method and Number of Respondents
CBCN	1) CBCN's 2017 Survey of ABC Patients – 180 Canadian ABC patient respondents – 65 had HR-positive breast cancer, of whom… ▪ 42 had HR-positive, HER2-negative breast cancer – None disclosed whether they were treated with ribociclib
	2) CBCN's 2012 ABC Patient and Caregiver Survey Report – 71 patient respondents – 16 caregiver respondents – None of the patients had experience with the treatment under review
	3) Interviews – 2 Canadians ▪ Patient 1 (Ontario): experience with ribociclib as a first-line treatment ▪ Patient 2 (Quebec): previously treated with surgery, radiation, and zoladex
	4) Review of current studies and grey literature
Rethink Breast Cancer	1) General survey of ABC patients – 74 women respondents ▪ 60 Canadians (Alberta, BC, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Quebec, and Saskatchewan)
	2) Survey of patients with ribociclib treatment experience for HR-positive, HER2-negative advanced or metastatic breast cancer – 26 women respondents ▪ 13 Canadians (Alberta, BC, Ontario, Quebec, and Saskatchewan)

Patient Group	Information Gathering Method and Number of Respondents
	▪ 17 patients were premenopausal, of these patients: o 17 patients received ribociclib plus an AI o 9 patients received ribociclib plus an AI and LHRH agonist o 9 received ribociclib as initial endocrine therapy

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with HR-positive, HER2-negative ABC

The CBCN's 2017 survey highlighted the key concerns of the 65 respondents with HR-positive breast cancer (42 were also HER2-negative) to include pain management, treatment initiation as early as possible following diagnosis, access to hormone therapy and targeted therapies over chemotherapy, and management of chemotherapy side effects. Majority of these respondents experienced metastases to their bones, liver, and lungs; in addition, a small fraction (two patients) had experienced metastases to their brain as well. To determine the physical impact of ABC, patients were asked what impact cancer-related symptoms had on their quality of life in the 2012 survey. Namely, 54% and 37% of patients reported that fatigue and pain resulted in a significant or debilitating impact, respectively. The social impact of ABC was reported from CBCN's 2017 survey responses; 12% were employed full-time at the time of the survey compared to 47% of respondents being employed full-time at the time of diagnosis; 74% of respondents experienced an impact on their mental health as a result of their diagnosis; and 40% reported a large negative impact on their finances. Additionally, the CBCN's 2012 survey reported significant restrictions with the ability to exercise (49%), pursue hobbies and personal interests (42%), participate in social events and activities (41%), and spend time with loved ones (22%). Of note, quality of life was identified to be very important for metastatic patients who regularly acknowledge the importance of having energy to attend their children's activities and to spend time with family and friends. Additional experiences mentioned by patients included guilt, the feeling of being a burden on caregivers, fear of death, poor body image, not knowing what functionality will be lost and what will happen to children, fear of impact of the cancer and loss of a parent on children, loss of support of loved ones, and martial stress/loss of fidelity and affection from partner. The physical and social impact of ABC is summarized in one patient's own words— *"I'm 43 now and I will be in treatments for the rest of my life. I have a very difficult time still trying to figure out how to move forward while taking advantage of all the wonderful moments I still have. I have no choice but to continue to battle this war that my body has bombarded my family and me with… the most difficult aspect is planning for my mortality and trying to keep my chin up and not burden my family" (Patient, 2017 Survey).*

Rethink Breast Cancer asked patients to rate the impact of ABC symptoms on their quality of life and to rate how symptoms associated with breast cancer have impacted their day-to-day activities on a scale from 1 (no impact) to 5 (significant impact). Fatigue was reported to have the most severe impact with an average score of 3.5 (n=68, 92%) followed by bone pain, which had an average score of 2.7 (n=70, 95%). Respondents indicated that

the greatest impact among daily activities was on their ability to work with an average score of 3.99 (n=70, 95%) followed by their ability to sleep 3.46 (n=72, 97%).

3.1.2 Patients' Experiences with Current Therapy for HR-positive, HER2-negative ABC

Among the 65 HR-positive breast cancer patient respondents of CBCN's 2017 survey, most of the patients had been treated with surgery (n=56), 48 patients had undergone radiation therapy, 48 patients had received hormone therapy, and 51 patients had been previously treated with chemotherapy. The results of CBCN's review of grey literature and current studies found that 80% of breast cancer patients experienced a financial impact due to their illness, 44% of patients used their savings, and 27% acquired debt to cover costs. Accordingly, the CBCN's 2012 survey reported that nearly one third of patients noted that the cost of medication and alternative treatments (e.g., massage, physiotherapy, etc.) and the required time to travel to treatment sessions had a significant or debilitating impact on quality of life. Additionally, 24% of patients indicated that travel costs had a significant or debilitating impact on their quality of life. Furthermore, 53% of patients with children or other dependents reported that there is minimal or no access to appropriate care for their dependents for when the patient is experiencing debilitating cancer-related symptoms. Similarly, the 2017 survey reported that 86% of HR-positive ABC patients indicated that the cost of prescription medications had a significant or some impact on their treatment decision-making and quality of life. Additionally, failure to qualify for work insurance, inability to change employers due to insurance loss, and the prohibitive cost of new treatment options were mentioned as other barriers.

The Rethink Breast cancer survey asked patients to list the treatments they have received since their diagnosis. All 26 patients responded and femara (Letrozole) was the most common treatment received. All reported treatments and the number and percentage of patients with respective treatment experience are listed in Table 3.2.

Table 3.2 Treatment experience of HR-positive, HER2-negative ABC, modified from Rethink Breast Cancer

Treatments Received	n (%)	Treatments Received	n (%)
Femara (Letrozole)	22 (84.6%)	Fulvestrant (Faslodex)	3 (11.5%)
Tamoxifen (Nolvadex)	10 (38.5%)	Exemestane (Aromasin)	3 (11.5%)
Zoladex (Goserelin)	8 (30.8%)	Pamidromate (Aredia)	2 (7.7%)
Anastrozole (Arimidex)	5 (19.2%)	Cyclophosphamide (Cytoxan)	2 (7.7%)
Paclitaxel (Taxol)	4 (15.4%)	Denosumab (Xgeva)	2 (7.7%)
Capecitabine (Xeloda)	3 (11.5%)	FEC- combination of 5-fluorouracil, epirubicin, cyclophosphamide	1 (3.8%)
Palbociclib (Ibrance)	3 (11.5%)	Docetaxel (Taxotere)	1 (3.8%)

Treatments Received	n (%)	Treatments Received	n (%)
Doxorubicin (Adriamycin)	3 (11.5%)	Trastuzumab (Herceptin)	1 (3.8%)
Leuprolide (Lupron)	3 (11.5%)	Zoledronic acid (Zometa)	1 (3.8%)

Note: percentages were manually calculated based on the reported total of 26 respondents and n reported for each treatment.

Patients were additionally asked which line of therapy they were receiving; of the 26 patient respondents, nine were on first-line treatment, three were on second-line treatment, three were on third-line treatment or higher, and three were receiving treatment after recurrence. It was noted that one patient had no evidence of disease for less than six months, three patients had no evidence of disease for six to twenty-four months, and four patients did not know or did not respond. Of note, the specific treatments that elicited these responses were not specified. Regarding side effects, fatigue was most commonly reported among these treatments (88%, n=24), followed by low blood cell counts (58%) and insomnia (54%). Additionally, fatigue was most commonly noted by respondents as the most difficult side effect to tolerate; although, insomnia, hair loss, joint pain, nausea, and back pain were also mentioned by multiple respondents.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for Ribociclib in Combination with an AI and LHRH Agonist

The key factors influencing treatment decision-making of HR-positive breast cancer patients according to CBCN'S 2017 survey follows:

1. Treatment effectiveness—how well the treatment stabilized their disease and delayed disease progression.

2. Prolonging life without sacrificing quality of life—ability to maintain productive, active lives with minimal disruption to daily routines.

3. Side effect management—minimizing risk while stabilizing disease.

4. Cost and accessibility of treatments—affordability and ease of treatment accessibility.

Extending OS and quality of life were highlighted by the CBCN to be values of patients with ABC. The CBCN noted that the value of extending OS to patients cannot be overestimated. Patients living with ABC are aware that their advanced disease will progress with worsening symptoms until death; thus, they embrace opportunities to try new treatments with demonstrated efficacy. Quality of life was also noted to be very important; patients regularly acknowledge the importance of having energy to attend their children's activities and to spend time with family and friends.

According to the CBCN's 2017 survey, treatment efficacy was reported to be critical to HR-positive ABC patients. Almost all respondents (99%) indicated that OS was very important or important in terms of making treatment decisions and 98% of respondents indicated that progression-free survival (PFS) of six months or more would influence their treatment decisions. Furthermore, 83% and 69% responded that PFS of three to five months and less than three months, respectively, would be very important as well. All of the HR-positive ABC patients felt that quality of life was very or somewhat important when considering

treatment options; accordingly, survival and quality of life were commonly mentioned as important factors regarding treatment decisions as stated in the following patient statements:

- *"The most important factors for me are progression free survival and quality of life." (Patient 2017 Survey)*
- *"Anything to prolong my survival and maintain quality of life." (Patient 2017 Survey)*
- *"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." (Patient 2017 Survey)*
- *"I want to live as long as possible with a good quality of life." (Patient 2017 Survey)*

CBCN's 2012 and 2017 surveys asked patients their willingness to tolerate treatment side effects. Almost two-thirds of patients indicated that fatigue, nausea, depression, problems with concentration, memory loss, diarrhea, and insomnia with some or moderate impact on one's quality of life would be acceptable, and approximately one quarter of patients indicated that these symptoms eliciting a strong or debilitating impact would be considered acceptable. Moreover, 70% of patients indicated that pain of some or moderate impact on one's quality of life would be considered acceptable, and 27% of patients indicated that pain with a strong or debilitating impact would be acceptable. Overall, majority of respondents indicated that they were willing to somewhat accept pain as a treatment side effect. Patients were asked the side effect level and the amount of impact on one's quality of life that would be worthwhile if it extended PFS by six months; patients responded by stating that this can only be determined case by case. CBCN's 2012 survey, asked patients about their willingness to tolerate risk with a new treatment. Thirty-four percent indicated they were willing to accept serious treatment risk if it would control disease; 45% were willing to accept some treatment risk; and 21% were very concerned and felt less comfortable with serious treatment risks. Overall, the CBCN data collection demonstrated that it is imperative that all women with HR-positive breast cancer have access to and the option of taking various drugs. Most patients are well aware of the treatment adverse effects and want to make a personal choice that is most suited for themselves. This is detailed in the patients' own words in the following quotations:

- *"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 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 also commented on patients' expectation of treatment outcomes; however, CBCN did not specify the source of this information. CBCN stated that patients expect that the ribociclib and AI combination will extend OS and improve quality of life as compared to chemotherapy or other hormonal therapies with more significant toxicity profiles. CBCN also suggested that ABC patients are aware that symptoms will progress until death; thus, the value associated with the opportunity to try new effective treatments cannot be overestimated. They noted that treatments that alleviate cancer-related symptoms and have minimal side effects allow for patients to care for children and dependents, continue

with employment and earn income, spend time with loved ones, engage in social activities, travel, maintain friendships, and pursue personal interests.

Rethink Breast Cancer asked patients to evaluate the importance of various treatment outcomes on a scale of 1 (not important) to 5 (very important). All listed outcomes were considered important as each outcome was rated with an average score over 4.4. However, controlling disease and extending life expectancy were rated as the most important outcomes, which suggests that patient values prioritize health outcomes over immediate concerns such as reducing symptoms or managing side effects. Scoring of the importance of various treatment outcomes are detailed in Table 3.3.

Table 3.3 Scoring of the importance of various breast cancer treatment outcomes, modified from Rethink Breast Cancer

Importance of outcome	1 - not important	2	3	4	5 – very important	Average
Controlling disease	0.0%	0.0%	0.0%	1.4 %	98.6%	5.0
Reducing symptoms	1.4%	0.0%	13.7%	20.6%	64.4%	4.5
Maintaining quality of life	0.0%	0.0%	1.4%	13.7%	84.9%	4.8
Managing side effects	1.4%	1.4%	13.7%	20.6%	63.0%	4.4
Achieving NED (no evidence of disease)	1.4%	1.4%	0.0%	6.9%	90.3%	4.8
Extending life expectancy	0.0%	0.0%	0.0%	2.8%	97.2%	5.0

Note: percentages were rounded to one decimal place, three to four decimal places were reported in the original input provided by Rethink Breast Cancer.

Patients were asked if they would be willing to tolerate new side effects from new drugs to extend life expectancy on a scale of 1 (will not tolerate side effects) to 10 (will tolerate significant side effects). Among all responses, there was an average score of 7.66, which reflects the general willingness to tolerate side effects from new drugs to extend life expectancy and also supports the conclusion that patient values prioritize health outcomes.

3.2.2 Patient Experiences To Date with Ribociclib in Combination with an AI and LHRH Agonist

The CBCN interviewed two patients with treatment experience with the ribociclib, AI, and LHRH agonist combination for which, the patient profiles are summarized below. Notably, only Patient 1 received ribociclib as initial endocrine-based therapy.

Patient 1: 54 year old patient who has been on treatment for three months. She was able to access prescribed treatment through a clinical trial in Ontario. Ribociclib is the first treatment she has been prescribed for her ABC.

Patient 2: 46 year old patient who has been on treatment for five months. She was able to access treatment through a clinical trial in Quebec. She has previously been treated with surgery, radiation and zoladex (Goserelin).

Both patients expressed their personal satisfaction with the treatment and specifically noted that their oncologists were pleased with ribociclib's efficiency in stabilizing and controlling their disease. In their words this is summarized by the following quotations:

- *"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*
- *"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*

Both patients expressed that they found the side effects to be very minimal and none were intolerable. Patient 1 experienced mild nausea and fatigue in the first month and occasional indigestion; and Patient 2 experienced thinning of hair and a lowered white blood cell count; however, she noted that neither of these conditions were intolerable. Side effects were accounted in the following patient quotations:

- *"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*

Both patients mentioned that chemotherapy would have been the likely alternative, and both expressed strong desires to avoid the side effects and intolerability of extensive chemotherapy regimens. Patient 1 mentioned that without ribociclib, she would have likely been immediately started on chemotherapy and potentially radiation. Patient 2 commented 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). Notably, patients did not comment on the financial impact of the treatment; however, they highlighted the impact that ribociclib has had on their quality of life and the ability to be productive. Patient 1 stated that during the time between diagnosis and the start of ribociclib treatment she was no longer physically active; previously, she was able to go on 75 kilometre bike rides. Following treatment, she is active again and has resumed cycling. The positive impacts of ribociclib is detailed in the patients' own words below:

- *"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

Rethink Breast Cancer's survey specific to ribociclib treatment experience for HR-positive, HER2-negative advanced or metastatic breast cancer received responses from 26 women. Among the 26 respondents, 17 were premenopausal and of these respondents, all received ribociclib in combination with an AI (n=17), nine received ribociclib in combination with a LHRH agonist and AI, and nine received ribociclib as initial endocrine therapy. However, the input mostly reported the responses of the four patients detailed below. Of note, the line of treatment Patient A received the ribociclib combination is unknown.

- *Patient A is from Quebec. She has new primary inflammatory stage IV breast cancer. She received ribociclib for 0-3 months in combination with femara and zoladex. She developed severe liver toxicity and had to discontinue the treatment.*
- *Patient B is from Ontario. She is receiving first-line treatment. She has received ribociclib for 6-12 months in combination with femara and zoladex. She required a dose reduction from 600mg to 400mg. She has also been treated with pamidromate (Aredia).*
- *Patient C is from the United States. She is receiving first-line treatment. She has received ribociclib for 0-3 months in combination with anastrozole, leuprolide, and zoladex.*
- *Patient D is from the United States. She is receiving second-line treatment. She has received ribociclib for more than one year in combination with femara and tamoxifen. She has also been treated with tamoxifen.*

Patients A, B, and D required financial assistance due to costs associated with their breast cancer and its treatment. In comparison to other treatments, patients were asked to rate the change to their quality of life on ribociclib compared to other treatments they had received on a scale of 1 (much worse) to 5 (much better). Patient D rated every category a 5 and commented that "This is my miracle drug!". Patient B rated every category a 5 except for the ability to work (4) and the ability to sleep (1). Patient A gave a range of scores from 1 to 4. Patient C declined to answer the questions because she could not make a comparison of ribociclib to other therapies. The detailed scoring of the change to quality of life is found in Table 3.4.

Table 3.4. Scoring of the change to quality of life with the ribociclib, AI, LHRH agonist combination compared to other therapies, modified from Rethink Breast Cancer

Change to quality of life on ribociclib	1 – much worse	2	3	4	5 – much better	Average
Metastatic cancer symptoms	0.0%	0.0%	33.3%	0.0%	66.7%	4.3
Drug side effects	0.0%	33.3%	0.0%	0.0%	66.7%	4.0
Maintaining quality of life	0.0%	33.3%	0.0%	0.0%	66.7%	4.0
Controlling disease progression	0.0%	0.0%	0.0%	33.3%	66.7%	4.7
Ability to work	33.3%	0.0%	0.0%	33.3%	33.3%	3.3
Ability to sleep	33.3%	0.0%	33.3%	0.0%	33.3%	3.0
Ability to drive	0.0%	33.3%	0.0%	0.0%	66.7%	4.0

Change to quality of life on ribociclib	1 – much worse	2	3	4	5 – much better	Average
Ability to perform household chores	0.0%	33.3%	0.0%	0.0%	66.7%	4.0
Ability to care for children	0.0%	33.3%	0.0%	0.0%	66.7%	4.0

Note: percentages were rounded to one decimal place, three decimal places were reported in the original input provided by Rethink Breast Cancer

When asked how much patients could tolerate the side effects associated with ribociclib on a scale of 1 (completely intolerable) to 10 (completely tolerable), Patient A said 5, Patient B said 9, and Patients C and D said 10, which amounts to an average score of 8.5 and demonstrates considerable tolerability. When asked about their experience on ribociclib, all four respondents provided the following comments:

- *"We saw very quick response (improvement) in the appearance of the affected breast from the inflammatory breast cancer. Unfortunately my liver did not tolerate the medication."—Patient A*
- *"Extended my quality of life."—Patient B*
- *"I have no significant side effects. My tumor markers have dropped every month I am on Kisqali. I'm having first post-diagnosis scans since starting Kisqali today, but my oncologist thinks I'm see significant shrinkage."—Patient C*
- *"Great! I can still function and am pretty much normal! I have been on Kisqali for almost 2 years now! It's my miracle drug!"—Patient D*

Regarding patient access to ribociclib, 77% of respondents (n=26) did not report any difficulties accessing ribociclib; however, several noted that ribociclib was only a treatment option due to participation in a clinical trial. Palbociclib (Ibrance) and chemotherapy were the only alternatives suggested by doctors if the respondents were unable to access ribociclib. Moreover, 24 of 26 respondents said that ribociclib therapy as a pill made their treatment experience easier; although, one would have preferred less frequent shots and one said that it made no difference. Overall, respondents unanimously recommended ribociclib to other breast cancer patients; elaborations are accounted below:

- *"Yes! 100% I am confident that this drug is extending my life significantly without impacting my quality of life."*
- *"I am convinced that I am alive today because of Kisqali."*
- *"Freedom. The side effects are a bit challenging at first, but it gets better. The dose can easily be adjusted for neutropenia. Better quality of life."*
- *"I think this drug has proven efficacy to prolong disease progression and this is giving me extra precious time to love and spend with my daughter and my family."*
- *"It's easy to take, the side effects go away quickly, and it almost put me in NED. It's totally worth taking and should be the first line of treatment, especially for us metastatic folks."*
- *"It was like a miracle... just take my tablets daily and live a fairly normal life. That is what I have done. I am still here to tell my story, and hope I will be around for a few more years."*

3.3 Companion Diagnostic Testing

Not applicable.

3.4 Additional Information

None to report.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The PAG 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 **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Clarity on eligible patient population

Economic factors:

- Additional healthcare resources for monitoring and management of adverse events

Please see below for more details.

4.1 Currently Funded Treatments

PAG noted that the MONALEESA-7 trial compared ribociclib plus ET (tamoxifen, letrozole, or anastrozole) to ET.

Various AI are available for initial treatment of advanced or metastatic disease in HR-positive, HER2-negative breast cancer. These include anastrozole, exemestane and letrozole. Palbociclib plus letrozole is also available in almost all jurisdictions while ribociclib (in combination with letrozole) as an initial endocrine-based therapy is under provincial consideration. Abemaciclib in combination with an AI or fulvestrant was also recently reviewed at pCODR and received positive conditional reimbursement recommendations.

PAG is seeking information comparing ribociclib to abemaciclib and palbociclib - is one better than the others and under what circumstances would ribociclib be preferred to abemaciclib or palbociclib or vice-versa?

4.2 Eligible Patient Population

PAG noted that this is a large patient population.

The MONALEESA 7 trial excluded patients with inflammatory breast cancer. PAG is also seeking information on whether results with ribociclib would be generalizable to men with metastatic breast cancer or HER-2 positive breast cancer (e.g., HR-positive, HER2-positive metastatic breast cancer who are not eligible for further anti-HER2 treatments).

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

- adding ribociclib for patients who are already on an endocrine therapy (e.g., anastrozole or letrozole) but not yet progressed
- use with other AI
- switching patients who are already on other ET but not yet progressed to ribociclib
- switching ribociclib with abemaciclib or palbociclib for the respective indications, if patient is intolerant to one

- continuing treatment if there is oligoprogression

If recommended for reimbursement, patients currently receiving single agent ET, would need to be addressed on a time-limited basis.

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

4.3 Implementation Factors

Ribociclib and palbociclib are taken daily for 21 days followed by 7 days off treatment while letrozole, anastrozole, and abemaciclib is taken daily continuous. PAG has concerns that the dosing of ribociclib being different than letrozole, anastrozole, and abemaciclib 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.

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. EKG monitoring would be required before treatment initiation, then at day 14 of cycle 1, and then prior to cycle 2.

As ribociclib may be added on to existing therapy, there may be a large budget impact given the large number of patients with estrogen-receptor positive, HER2-negative breast cancer and the high cost of the combination compared to letrozole or anastrozole alone and other AIs. There will be additional pharmacy resources required for adding an additional agent in the same class as abemaciclib and palbociclib to an aromatase inhibitor alone.

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.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate sequencing of all available treatments for HR-positive, HER2-negative ABC:

- PAG noted that ribociclib plus fulvestrant is also under review at pCODR and is seeking guidance on preference for ribociclib plus an AI or fulvestrant in this endocrine-naïve/sensitive advanced breast cancer setting.
- Is there a preference for CDK 4/6 inhibitor (e.g., ribociclib, abemaciclib, or palbociclib) or are they considered therapeutically equivalent?

- What treatments can patients receive following ribociclib plus an AI?
- Is there evidence to support re-treatment with ribociclib or another CDK 4/6 inhibitor in patients whose disease progressed on or after ribociclib?
- How should everolimus plus exemestane be sequenced?

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.

4.5 Companion Diagnostic Testing

HER2 testing is already available.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One joint input submission from two clinicians on behalf of CCO provided input on the use of ribociclib in combination with an AI and a LHRH agonist for the treatment of pre- and peri-menopausal women with HR-positive, HER2-negative ABC as initial ET. Current therapies for the indication under review include various AIs such as anastrozole, exemestane, and letrozole. Furthermore, palbociclib plus letrozole is available in almost all jurisdictions, ribociclib plus letrozole as an initial ET is under provincial consideration, and abemaciclib plus an AI or fulvestrant recently received a positive conditional reimbursement recommendation following pCODR review. Based on the results of the MONALEESA-7 trial, it was noted that the ribociclib combination with an AI and a LHRH agonist is superior to endocrine therapy alone and exhibits an acceptable toxicity profile; thus, the CCO clinicians expect the treatment combination to be widely used in clinical practice. Despite availability of other ET options for pre- and peri- menopausal women with HR-positive, HER2-negative ABC, the CCO clinicians indicated they would administer the ribociclib, AI, and LHRH agonist combination in the first-line setting over abemaciclib, palbociclib, and ribociclib plus fulvestrant based on the clinical trial evidence. Moreover, the CCO clinicians felt that there is limited evidence to extend the use of ribociclib plus an AI to HER2-positive patients but would consider administering ribociclib plus an AI and LHRH agonist in male breast cancer patients. Upon progression with ribociclib and fulvestrant, presumably in the second-line setting, therapy options would include everolimus plus exemestane or chemotherapy. Selection of the appropriate therapy would depend on the availability of everolimus, prior treatment with endocrine therapy, and clinical features that may suggest the preferability of chemotherapy. Contraindications were reported as per the ribociclib monograph; namely, ribociclib is contraindicated in patients with hypersensitivity to the drug or composite ingredients in the formulation and in patients with or at risk of pathological prolongation of the QT interval. Further, biomarker testing for HR and HER2 mutations were noted to be currently funded and part of standard care.

Please see below for details from the clinician input.

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

The CCO clinicians stated that ribociclib in combination with an AI and a LHRH agonist is a new treatment option for pre- and peri- menopausal women with HR-positive, HER2-negative metastatic breast cancer in the first-line setting.

5.2 Eligible Patient Population

Despite the availability of other ET options for pre- and peri- menopausal women with HR-positive, HER2-negative ABC, the clinicians stated that the results of the MONALEESA-7 trial support the inclusion of ribociclib to the endocrine backbone. Namely, they noted the superiority of treatment with ribociclib plus an AI and a LHRH agonist to ET alone and its potential to be widely used. Accordingly, the clinicians noted that the inclusion/exclusion criteria of the MONALEESA-7 are generalizable to clinical practice.

Implementation Questions: The eligibility criteria for the MONALEESA 7 trial included a specific patient population compared to the broader funding request. In clinical practice, is there evidence to extend the use of ribociclib plus an aromatase inhibitor to (provided all other eligibility criteria are met):

a) HER2-positive breast cancer (e.g., HR positive, HER-2 positive metastatic breast cancer

who are not eligible for further anti-HER2 treatments)

The CCO clinician input stated that there is limited evidence in clinical practice to extend the use of ribociclib with an AI to HER2-positive breast cancer patients; thus, they would not treat these patients with this therapy at this time.

b) Male breast cancer

The CCO clinicians stated that males should have access to the ribociclib and AI combination as they would consider administering ribociclib with an AI plus a LHRH agonist to male breast cancer patients.

5.3 Relevance to Clinical Practice

All the clinicians who provided input on behalf of CCO had experience administering ribociclib plus an AI and a LHRH agonist. They stated that the treatment would be used in the first-line setting in the same patient population as per the MONALEESA-7 trial. It was noted that the ribociclib combination with an AI and a LHRH agonist is superior to endocrine therapy alone and exhibits an acceptable toxicity profile. Contraindications that were reported for ribociclib according to the drug monograph included:

- Patients with hypersensitivity to this drug or to any ingredient in the formulation.
- Patients with untreated congenital long QT syndrome, a QTcF interval of ≥450 milliseconds at baseline, and those at significant risk of developing QTc prolongation.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

Implementation Questions: Please consider if there is evidence to support the optimal sequencing of treatment for patients with HR positive HER2-negative breast cancer. In clinical practice, if ribociclib plus an aromatase inhibitor was available,

a) In what clinical scenarios would ribociclib or abemaciclib or palbociclib be the preferred treatment in the endocrine-naïve setting? Please comment on the preference considering patient preference, efficacy, safety, and administration.

The CCO clinicians supported the use of ribociclib over palbociclib and abemaciclib in the endocrine-naïve setting. Abemaciclib was reported to have more toxicities and, although the toxicity profile of palbociclib is the most acceptable, the results of MONALEESA-7 support the use of ribociclib plus an AI and a LHRH agonist in the first-line setting in this population.

b) In what clinical scenarios would ribociclib plus an aromatase inhibitor versus ribociclib plus fulvestrant be the preferred treatment in the endocrine-naive setting?

The CCO clinicians stated that ribociclib plus an AI and a LHRH agonist would be the preferred treatment in the endocrine naïve setting over ribociclib plus fulvestrant based on the clinical trial evidence for this patient population.

c) What treatment options would be available to patients upon progression of ribociclib plus fulvestrant (e.g., everolimus plus exemestane, or chemotherapy)?

The CCO clinicians noted that upon progression with ribociclib and fulvestrant, presumably in the second-line setting, therapy options would include everolimus plus exemestane or chemotherapy. Selection of the appropriate therapy would depend on the availability of

everolimus, prior treatment with endocrine therapy, and clinical features that may suggest the preferability of chemotherapy.

5.5 Companion Diagnostic Testing

The CCO clinicians stated that biomarker testing for HR/HER2 mutations are currently funded and part of standard of care; thus, this testing is currently available.

5.6 Additional Information

None to report.

6 SYSTEMATIC REVIEW

6.1 Objectives

The objective of the systematic review was to assess the efficacy and safety of ribociclib combined with an AI and a LHRH as initial endocrine-based treatment in pre- and peri-menopausal women with HR-positive, HER2-negative ABC.

Supplemental issues relevant to the pCODR review and to the PAG were identified while developing the review protocol and are outlined in section 7:

- Summary and Critical Appraisal of a Sponsor-submitted ITC

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 6.1. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6.1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCT	Pre- or peri-menopausal or post-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer Subgroups of interest: • Time since adjuvant therapy • Recurrence on previous treatment (versus not) • Adjuvant tamoxifen versus AI	Ribociclib 600mg by mouth once daily for 21 days, followed by 7 days off treatment, combined with an AI and a LHRH agonist, as initial endocrine-based therapy	Endocrine therapy alone: • AI (e.g., anastrazole, exemestane, letrozole) • Selective estrogen receptor modulators (e.g. tamoxifen) CDK 4/6 inhibitor + AI: • Palbociclib • Abemaciclib CDK 4/6 inhibitor + fulvestrant**: • Palbociclib • Abemaciclib Chemotherapy	***Efficacy:*** • **OS** • PFS • ORR • TTR • DOR • **HRQOL** • **Time-to-chemotherapy** ***Harms:*** • AEs • SAEs • WDAEs • Mortality Notable harms: QT prolongation, hepatotoxicity, neutropenia, fatigue

Abbreviations: AEs=adverse events; AI=aromatase inhibitor; CDK – cyclin dependent kinase; HER2 – human epidermal growth factor receptor 2; HRQOL=health-related quality of life; LHRH=luteinizing hormone-releasing hormone; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RCT= randomized controlled trial; SAEs=serious adverse events; TTR=time-to-response; WDAEs=withdrawals due to adverse event.

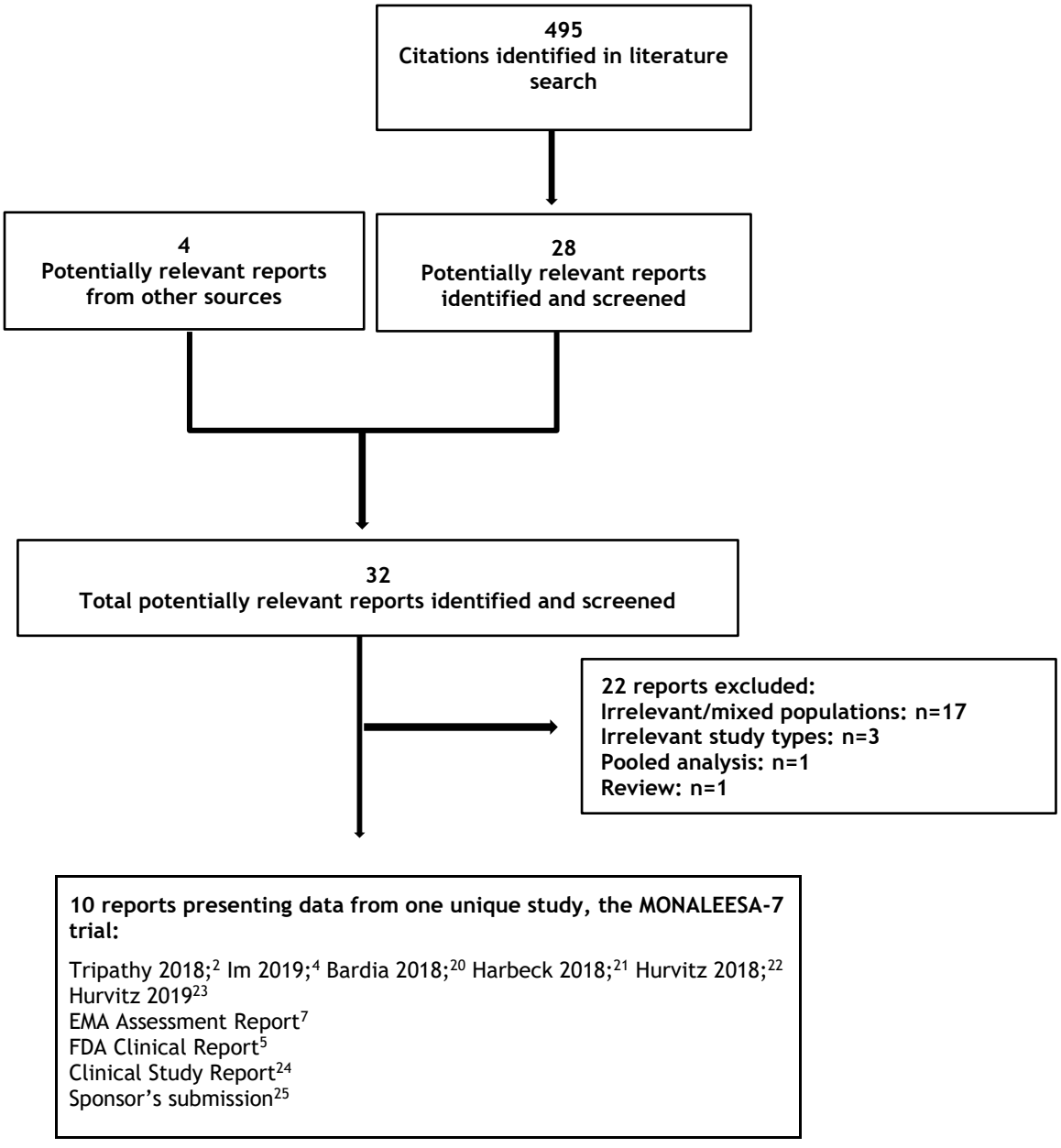
Notes:
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)
** These were identified as relevant comparators after the protocol was developed during the review process.

6.3 Results

6.3.1 Literature Search Results

Of the 32 potentially relevant reports identified, eight reports were included in the pCODR systematic review[2,4,20-25] and 22 were excluded. Studies were excluded because they included irrelevant or mixed populations,[26-42] represented a pooled analysis,[43] irrelevant study types,[44-46] or a review. [47]Figure 6.1 illustrates the PRISMA flow diagram for the study selection process.

Figure 6.1. PRISMA Flow Diagram for Inclusion and Exclusion of Reports



Note: Additional data related to MONALEESA-7 were also obtained through requests to the sponsor by pCODR (Checkpoint meeting additional information request)[6]

6.3.2 Summary of Included Studies

One phase 3 RCT (MONALEESA-7) that compared ribociclib plus an AI to placebo plus an AI in pre- and peri-menopausal women with ABC was included in the systematic review; refer to tables 6.2 and 6.3 for a summary of trial and quality characteristics, respectively.

6.3.2.1 Detailed Trial Characteristics

Table 6.2: Summary of the MONALEESA-7 trial

Trial Design	Eligibility Criteria	Intervention and Comparator	Trial Outcomes
MONALEESA-7 (NCT02278120) Phase 3, DBRCT, placebo controlled Randomization 1:1 N randomized and treated = 672 188 sites, 30 countries (including Canada) Patient randomization dates: December 2014 to August 2016 Data cut-off: August 20, 2017 Final analysis date: December 21, 2020 Funding: Novartis Pharmaceuticals	Inclusion: • Females, age ≥18 to <60 years old • Pre- or peri-menopausal • ABC (locoregionally recurrent or metastatic) not amenable to curative therapy (surgery +/- RT) • Received (neo) adjuvant therapy for BC, but previous ET for ABC not permitted, except patients who received ≤ 14 days of TAM or a NSAI +/- GOS or only GOS ≤ 28 days for ABC prior to randomization. Patients were to continue treatment with the same hormonal agent plus GOS during study • Received up to one line of CT for ABC and discontinued 28 days before randomization • Histological and/or cytological confirmation of ER+ and/or PR+ BC, HER2(-) • Measurable disease, i.e. ≥1 measurable lesion as per RECIST version 1.1 criteria or- ≥1 predominantly lytic bone lesion • ECOG PS 0 or 1 Exclusion: • Received prior CDK4/6 inhibitor therapy • Inflammatory breast cancer at screening • Concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated BCC, SCC, NMSC, or curatively resected CC • Symptomatic visceral disease • CNS metastases • Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality	Intervention: Ribociclib 600 mg PO OD, days 1-21 of a 28-day cycle + GOS 3.6 mg SC implant on day 1 of 28-day cycle + NSAI (LET 2.5 mg PO OD or ANA 1 mg PO OD) or TAM 20 mg Comparator: Matching placebo + GOS 3.6 mg SC implant on day 1 of 28-day cycle + NSAI (LET 2.5 mg PO OD or ANA 1 mg PO OD) or TAM 20 mg	Primary: PFS Key Secondary: OS Other secondary: • ORR and CBR • TTR • DOR • Time-to-deterioration in ECOG PS • HRQOL • Safety/tolerability

Abbreviations: ABC=advanced breast cancer; ANA=anastrozole; BC=breast cancer; BCC=basal cell carcinoma; CBR=clinical benefit rate; CC=cervical cancer; CISH=chromosome in situ hybridization; CNS=central nervous system; CT=chemotherapy; DOR=duration of response; DBRCT=double blind randomized controlled trial; ECOG=Eastern Cooperative Oncology Group; EE2=ethinyl estradiol; ER+ = estrogen receptor positive; ET=endocrine therapy; EXE=exemestane; FISH=fluorescent in situ hybridization; FSH=follicle stimulating hormone; FULV=fulvestrant; GOS=goserelin; HER2(-)=human epidermal growth factor receptor-2 positive; HRQOL=health-related quality of life; LET=letrozole; LMP=last menstrual period; NMSC=non-melanoma skin cancer; NSAI=non-steroidal aromatase inhibitor; OD=once daily; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PMP=premenopausal; PO=orally; PR+ = progesterone receptor positive; PS=performance status; RECIST=response evaluation criteria in solid tumours; RT=radiation therapy; SC=subcutaneous; SCC=squamous cell carcinoma; SISH=silver-enhanced in situ hybridization; TAM=tamoxifen; TTR=time-to-response.

Sources: Tripathy 2018;[2] ClinicalTrials.gov[48]

Table 6.3: Select quality characteristics of the MONALEESA-7 trial

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-7 Sponsor-funded[a]	Ribociclib + AI or tamoxifen vs. placebo + AI or tamoxifen	PFS	N=660 for 329 PFS events to provide 95% power to detect an HR of 0.67 at a one-sided 2.5% level of significance[b]	N=672	IRT	Trial personnel remained blinded till database lock	DB matched placebo	Yes	Yes-for primary outcome	No	Yes

Abbreviations: AI=aromatase inhibitor; DB=double blind; HR=hazard ratio; IRT=interactive response technology; PFS=progression-free survival.

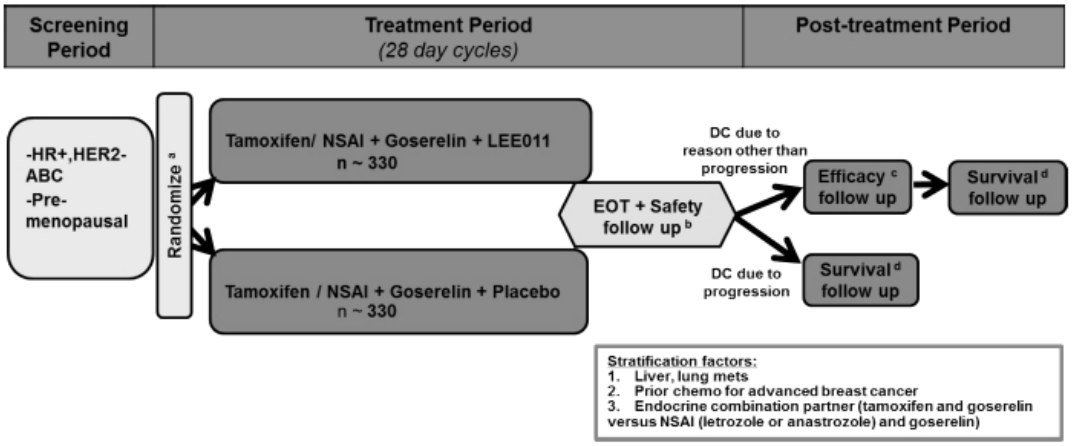
Notes:
[a] The sponsor (Novartis) was involved in all aspects of trial conduct including data collection, analysis, interpretation, and manuscript writing.
[b] The required sample size was based on the following assumption: median PFS of 9 months in placebo, recruitment of 33 patients per month over 18 months and loss to follow up for PFS of ~10% of patients.

Source: Tripathy 2018[2]

a) Trials

MONALEESA-7 is an international, multi-centre, placebo-controlled, double-blind, multicentre, phase 3, ongoing superiority trial that is being conducted in 188 sites in 30 countries including Canada (six Canadian sites; n=24).[2] The sponsor, Novartis Pharmaceuticals, funded the trial. Patients were randomized 1:1 to either ribociclib or placebo and were stratified by presence of lung or liver metastases (yes/no), prior chemotherapy for advanced disease (yes/no) and endocrine combination partner (tamoxifen/NSAI). The MONALEESA-7 trial design is depicted in Figure 6.2.

Figure 6.2: Trial design of the MONALEESA-7 trial



Source: Reprinted from The Lancet Oncology, 19(7), Tripathy D et al., Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial, pg. 904-915, Copyright (2018), with permission from Elsevier. [2]

The choice of endocrine combination partner was based on patients' previous (neo)adjuvant therapy or investigator or patient preference:

- patients who had received (neo)adjuvant ET were eligible to receive either NSAI plus goserelin or tamoxifen plus goserelin for ABC if 12 or more months had elapsed since the last dose of (neo)adjuvant therapy; or
- if tamoxifen was the last prior (neo)adjuvant therapy and the last dose was given within the last 12 months prior to randomization, then the patient was eligible to receive a NSAI plus goserelin for ABC; or
- if letrozole, anastrozole, fulvestrant, or exemestane were the last prior therapy and the last dose was given within the last 12 months prior to randomization, then the patient was eligible to receive tamoxifen plus goserelin for ABC.

Crossover to the other endocrine partner was not permitted during the trial, nor was crossover between NSAIs (letrozole to anastrozole or vice versa). Blinding was facilitated by use of a matching placebo, and all trial personnel involved with the trial and patients remained blinded until database lock (October 18, 2017).

Outcomes and Statistical Analyses

Tumour assessments were performed using computed tomography or magnetic resonance imaging at screening, every eight weeks during the first 18 months of the trial, and every 12 weeks thereafter until disease progression, death, withdrawn consent, lost to follow up, or patient/guardian decision.

Primary Outcome

The primary outcome was investigator-assessed PFS, and the primary efficacy analysis was planned for when approximately 329 PFS events had been documented. PFS was defined as the time from randomization to either the first documented disease progression per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1) or death from any cause. Assessment of PFS through a blinded

independent central review (BIRC) was used for supportive evidence of the primary endpoint. Data collected in the clinical database after a patient had withdrawn informed consent was not included in the efficacy analysis; however, death events were included if collected from public records (as long as local laws and patient informed consent permitted this to occur). PFS was censored if no events had occurred by the data cut-off date, and the censoring date used was the last adequate tumour assessment. If a PFS event was observed after two or more missing or non-adequate tumour assessments, then PFS was censored at the last adequate tumour assessment; however, if observed after a single missing or non-adequate assessment, the actual date of the PFS event was used.

The primary efficacy analysis was the comparison of PFS between the two treatment groups using a stratified log-rank test at a one-sided 2.5% level of significance.[7] The PFS HRs with two-sided 95% CIs were estimated using the stratified Cox proportional hazards model and survival distribution estimated using the Kaplan-Meier method and displayed graphically.[7]

Subgroup analyses of PFS were performed as long as the primary efficacy analysis was found statistically significant; prespecified subgroups considered relevant to this review included the following: endocrine combination partner (tamoxifen and goserelin vs. NSAI and goserelin), prior chemotherapy in the metastatic setting (yes vs. no), adjuvant or neoadjuvant chemotherapy (yes vs. no) in patients with no prior chemotherapy in the metastatic setting; hormonal agent in (neo)adjuvant setting (tamoxifen; NSAI and others; none), and prior (neo)adjuvant ET (none; yes: progression while on or within 12 months of end of adjuvant ET; progression > 12 months after end of adjuvant ET).

Secondary Outcomes

A hierarchical testing procedure was employed to account for multiple testing, whereby the key secondary outcome of OS would only be tested if the primary outcome of PFS was found statistically significant. If a statistically significant difference in PFS was observed, the trial was to proceed, and investigators and patients remained blinded to study treatment. All patients were continuously followed for OS until the final OS analysis, or earlier if OS reached statistical significance at any of the interim analyses. There were three interim analyses planned for OS: one at the time the primary analysis for PFS was performed (123 deaths expected), a second after approximately 189 deaths, and a third and final analysis after 252 deaths have occurred. A Kaplan-Meier analysis was employed to assess the distribution function, and the two treatment groups were compared using a stratified log rank test at a one-sided 2.5% level of significance. The type I error for testing of OS was controlled using an O'Brien-Fleming alpha spending function at the one-sided type I error of alpha=0.025.

Additional secondary outcomes were assessed but not included in the statistical hierarchy and included ORR (confirmed CR or PR), time-to-response (TTR; time from randomization to first documented complete or partial response), and duration of response (DOR; time from first documented complete or partial response to first documented progression or death due to the underlying cancer). ORR was tested using a Cochran-Mantel Haenszel chi-square test (with strata based on randomization factors), at a one-sided 2.5% level of significance. As a sensitivity analysis, these tests were also performed on the subset of patients with measurable disease.

HRQOL was as an exploratory endpoint and assessed using the EORTC QLQ-C30 (version 3.0), the EORTC-QLQ-BR23 (version 1.0) breast symptoms subscale, and

the EQ-5D—5L (version 4.0). The primary patient-reported outcome of interest was the time-to-10% deterioration in the global health status/QOL subscale of the EORTC-QLQ-C30. No formal statistical tests for HRQOL outcomes were performed. A definitive 10% deterioration was defined as a worsening in score by 10% or more when compared to baseline, with no later improvement above this threshold during the treatment period, or death due to any cause. No minimal clinical important difference (MCID) was specified for any of the HRQOL assessment instruments.

The EORTC-QLQ-C30 contains 30 items, including global health status/quality of life scale, five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain) and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial impact). The EORTC QLQ-BR23 includes an additional 23 items that are specific to breast cancer, with five multi-item scales assessing systemic therapy side effects, arm symptoms, breast symptoms, body image, and sexual functioning, as well as single items assessing sexual enjoyment, hair loss, and future perspective. All scales range in score from 0 to 100, and higher scores represent higher response (thus a high score for functioning represents high functioning while a high symptom score represents a high symptom burden). The EQ-5D-5L is a generic HRQOL scale consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), and five levels in each dimension. Patients choose one of five levels that best describe their health state: no problems, slight problems, moderate problems, severe problems, and extreme problems. The responses to the five dimensions are reflective of a specific health state corresponding to a population preference weighting for that state on a scale from 0 (death) to 1 (perfect health). A visual analogue scale (VAS) is also used to obtain an assessment of the patient's perception of their overall health status, on a scale from 0 to 100, with higher scores on the EQ-5D-5L indicative of better health status.

Safety was assessed at each study visit, the end of treatment and during the last 30 days after the last dose of study treatment. Adverse events were graded using the Common Terminology Criteria for Adverse Events version 4.03. ECG assessments were performed regularly, at screening, day 15 of cycle 1, days 1 and 15 of cycle 2, and day 1 of all subsequent cycles up to cycle 6, at the end of treatment.

Protocol Amendments

There were four protocol amendments that occurred during the trial.[7] The first, which occurred after 24 patients had been enrolled, involved changing the PFS assessment per BIRC from a supportive analysis of the primary outcome to a secondary outcome. The second amendment, after 372 patients had been enrolled, replaced a central radiology assessment by medical oncologist review with a standard BIRC assessment. Protocol amendment three, after 611 patients had been enrolled, included three items: the planned futility analysis was eliminated; the BIRC assessment of PFS was changed from a full read to an audit-based approach; and an exploratory endpoint, PFS2, was added. PFS2 was defined as time from randomization to progression on next line of therapy or death, whichever occurred first, to assess longer-term clinical benefit intermediate to PFS and OS. The fourth amendment, after 672 patients had been enrolled, removed the planned efficacy interim analysis of PFS that allowed the study to stop for superior efficacy after all patients had been randomized and approximately 80% (N=263) of PFS events had been documented, per local assessment.

b) Populations

MONALEESA-7 included females with HR-positive, HER2-negative ABC who were pre- or peri-menopausal at time of study entry; a total of 672 patients were randomized. Refer to Table 6.4 for more details.

Overall, the baseline characteristics of enrolled patients were well balanced between the trial treatment groups. Included patients had a median age of 43 years in the ribociclib group, and 45 years in the placebo group. At the time of study entry, all but one patient in each group had distant metastases. The most common sites of metastasis were the bone (74% of patients), visceral (57%) and lymph nodes (45%). Approximately 74% of patients had an ECOG performance status of 0 and with the exception of one patient, the rest had an ECOG performance status of 1. Non-de novo patients made up 60% of the trial population, and 54% of these patients had a disease-free interval of >12 months from diagnosis. There were approximately 40% of patients who had prior (neo)adjuvant ET, with 30% who had progression either on ET or within 12 months of stopping ET and approximately 9% having progressed more than 12 months after ET (for 1% of patients these data were missing). Prior chemotherapy for ABC was received in 14% of trial patients.

Table 6.4: Baseline characteristics of patients in the MONALEESA-7 trial

	Ribociclib group (n=335)	Placebo group (n=337)
Age, years	43 (25–58)	45 (29–58)
Race		
White	187 (56%)	201 (60%)
Asian	99 (30%)	99 (29%)
Black	10 (3%)	9 (3%)
Other or unknown	39 (12%)	28 (8%)
ECOG performance status		
0	245 (73%)	255 (76%)
1	87 (26%)	78 (23%)
2	0	1 (<1%)
Missing	3 (1%)	3 (1%)
Disease status at study entry		
Locally advanced	1 (<1%)	1 (<1%)
Metastatic	334 (100%)	336 (100%)
Hormone receptor status		
Oestrogen receptor positive	331 (99%)	335 (99%)
Progesterone receptor positive	290 (87%)	288 (85%)
Disease-free interval*		
Newly diagnosed disease	136 (41%)	134 (40%)
Existing disease	199 (59%)	203 (60%)
≤12 months	23 (7%)	13 (4%)
>12 months	176 (53%)	190 (56%)
Previous neoadjuvant or adjuvant endocrine therapy		
No	208 (62%)	196 (58%)
Yes	127 (38%)	141 (42%)
Progression ≤12 months after endocrine therapy	100 (30%)	105 (31%)
Progression >12 months after endocrine therapy	25 (7%)	35 (10%)
Data missing	2 (1%)	1 (<1%)

(Table 1 continues in next column)

	Ribociclib group (n=335)	Placebo group (n=337)
(Continued from previous column)		
Previous chemotherapy		
For advanced disease	47 (14%)	47 (14%)
Neoadjuvant or adjuvant only	138 (41%)	138 (41%)
None	150 (45%)	152 (45%)
Previous surgery (non-biopsy)		
Yes	202 (60%)	194 (58%)
No	133 (40%)	143 (42%)
Previous radiotherapy		
Yes	161 (48%)	183 (54%)
No	174 (52%)	154 (46%)
Metastatic sites		
0†	1 (<1%)	0
1	112 (33%)	117 (35%)
2	106 (32%)	99 (29%)
≥3	116 (35%)	121 (36%)
Site of metastases		
Soft tissue	25 (7%)	21 (6%)
Bone	251 (75%)	247 (73%)
Bone only	81 (24%)	78 (23%)
Visceral‡	193 (58%)	188 (56%)
Lymph nodes	142 (42%)	158 (47%)
Skin	8 (2%)	8 (2%)

Data are median (range) or number (%). Some percentages do not add up to 100 because of rounding. ECOG=Eastern Cooperative Oncology Group. *Newly diagnosed disease included patients with no first recurrence or progression, or first recurrence or progression within 90 days of diagnosis with no previous anticancer medication. For patients with existing disease, disease-free interval was the time from initial diagnosis to first recurrence or progression. †Patients with locoregionally recurrent (non-metastatic) disease were also eligible. ‡Liver, lung, and any other metastatic site except for soft tissue, bone, skin, and lymph nodes.

Table 1: **Demographics and baseline characteristics**

Source: Reprinted from The Lancet Oncology, 19(7), Tripathy D et al., Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial, pg. 904-915, Copyright (2018), with permission from Elsevier.[2]

c) Interventions

MONALEESA-7 evaluated ribociclib at a dose of 600 mg orally once daily, for days 1 to 21 of a 28-day cycle. Patients received goserelin (3.6 mg by subcutaneous implant) on day 1 of the 28-day cycle and either tamoxifen (20 mg orally once daily) or a NSAI (letrozole 2.5 mg orally once daily or anastrozole 1 mg orally once daily). Treatment continued until there was disease progression, unacceptable toxicity, death or discontinuation for any reason. The median duration of treatment exposure (interquartile range; IQR) at the time of the primary efficacy analysis was 15.2 (9.0 to 19.8) months in the ribociclib group and 12.0 (4.6 to 17.4) months in the placebo group. The median relative dose intensity was 94% (IQR: 70% to 99%) for the 333 patients who received ribociclib (median dose intensity 563.9 mg) and 100% (IQR: 99% to 100%) for the 335 patients who received placebo (equivalent median dose intensity of 600.0 mg).

Patients who discontinued ribociclib or goserelin could remain on study; however, those who discontinued ET were considered to be at the end of study treatment. Dose reductions were allowed for patients treated with ribociclib experiencing adverse events (two levels, first to 400 mg then to 200 mg) but were not permitted for tamoxifen, NSAI or goserelin. Dose interruptions occurred in 255 (77%) of 333 patients who received ribociclib and in 126 (38%) of the 335 patients who received placebo. Dose reductions occurred in 117 (35%) patients who received ribociclib and 21 (6%) who received placebo, most commonly for adverse events (in 104 [31%] and 17 [5%] patients, respectively).

The percentage of patients receiving subsequent anti-neoplastic therapy after discontinuing study drug was similar between the ribociclib (151 patients, 69%) and placebo (205 patients, 73%) groups.[4] The most common subsequent therapies were chemotherapy alone (22% versus 29%, respectively) and ET alone (22% versus 20%, respectively). Use of subsequent CDK 4/6 inhibitors was lower in the ribociclib group than the placebo group (10% versus 19%, respectively).[4]

Concomitant medications were generally allowed in the trial to manage adverse events and symptoms, including supportive therapy (e.g., anti-diarrhea medications, analgesics, anti-emetics), and to treat other unrelated conditions that the patient may have. Use of systemic corticosteroids, which may interact with ribociclib via CYP3A, was only allowed for short durations (<5 days) and lower doses (dexamethasone equivalent of 4mg daily). Palliative radiotherapy was permitted as long as it was not delivered to a target lesion and did not encompass >25% of irradiated bone marrow. A specific list of additional medications could be excluded from patient use if necessary, at the discretion of the investigator. This list included a number of drugs that interfere with CYP3A 4/5 isozymes, as well as other drugs that may cause issues with drug interactions or increase risk of QT prolongation.

d) Patient Disposition

MONALEESA-7 is an ongoing trial, and as of the primary efficacy analysis data cut-off date, the median follow-up time of patients was 19.2 months. At this time, 48% of patients in the ribociclib group and 64% in the placebo group had discontinued treatment (refer to Table 6.5). The most common reason for discontinuing treatment in both the ribociclib and placebo groups was progressive disease (in 36% versus 52% of patients, respectively). There were two patients (1% of study population) in the ribociclib group and no patients in placebo who were lost to follow up.

The Full Analysis Set (FAS) consisted of all randomized patients. Patients were analyzed according to the treatment and stratum they were assigned to at randomization. The FAS was the primary analysis set for efficacy analyses.

The Safety Analysis Set (SAS) consisted of all patients who received at least one dose of any component of study treatment. Patients were analyzed according to the treatment actually received, which refers to the randomized treatment unless the alternative treatment was received throughout the study.

The Per-protocol Set (PPS) included the subset of patients from the FAS without a major protocol deviation who took at least one dose of study treatment.

Overall, 43% of trial patients had at least one protocol deviation.[7] The number of protocol deviations resulting in exclusion from the PPS was low, with no imbalance between the two treatment groups; nine patients (1.3%) had protocol deviations that lead to exclusion from the PPS, and all of these were due to selection criteria not being met.

Based on the most recent data cut-off date for the trial (November 30, 2018), 65% of patients in the ribociclib group and 83% of patients in the placebo group had discontinued treatment, primarily due to progressive disease (PD) (52% versus 68% of patients, respectively).[4]

Table 6.5: Patient disposition in the MONALEESA-7 trial

Patient Disposition	MONALEESA-7	
	Ribociclib	Placebo
Screened, N	905	
Randomized, n (%)	335 (100)	337 (100)
Randomized and treated, n (%)	335 (100)	337 (100)
Primary Efficacy Analysis - August 20, 2017		
Treatment Ongoing	174 (52)	121 (36)
Discontinued treatment	161 (48)	216 (64)
Reason for end of treatment, n (%)		
-progressive disease	122 (36)	174 (52)
-patient/guardian decision	14 (4)	8 (2)
-adverse event	12 (4)	10 (3)
-physician decision	8 (2)	19 (6)
-death	3 (1)	3 (1)
-protocol deviation	0	2 (1)
-lost to follow up	2 (1)	0
Second Interim OS Analysis - November 30, 2018		
Treatment Ongoing	116 (35)	57 (17)
Discontinued treatment	219 (65)	280 (83)
Reason for end of treatment, n (%)		
-progressive disease	173 (52)	230 (68)
-patient/guardian decision	20 (6)	10 (3)
-adverse event	11 (3)	13 (4)
-physician decision	10 (3)	22 (7)
-death	3 (1)	3 (1)
-protocol deviation	0	2 (1)
-lost to follow up	2 (1)	0
Full analysis set, n (%)	335 (100)	337 (100)
Safety analysis set, n (%)	335 (100)	337 (100)

Abbreviations: OS=overall survival.

Source: Tripathy 2018;[2] Im 2019[4]

e) Limitations/Sources of Bias

Overall, the MONALEESA-7 trial was well conducted; however, the lack of an active comparator is a limitation of the trial. There are two other CDK 4/6 inhibitors currently marketed in Canada: palbociclib and abemaciclib. No direct evidence comparing ribociclib with these two drugs was identified through the review process. Additionally, a comparison to chemotherapy may have provided further context with respect to harms, as the harms caused by ET are relatively mild compared to cytotoxic chemotherapy. Though chemotherapy tends to be reserved for more severely ill patients, this still represents a gap in knowledge about ribociclib. The sponsor provided an ITC that compared ribociclib to relevant comparators, and this can be found in Section 7 of this report.

MONALEESA-7 was both randomized and double blinded; and steps were taken during randomization to maintain allocation concealment, and a matched placebo was used to facilitate blinding. There was a large imbalance in events of neutropenia between the ribociclib and placebo groups and, given that this is a known side effect of CDK 4/6 inhibitors, this could have alerted investigators and patients to identify the assigned treatment. Loss of blinding is less likely to have impacted objective assessments such as OS, PFS and ORR but may have impacted outcomes like HRQOL and assessment of harms, including investigator assessment of whether they were drug-related or not.

A hierarchical testing procedure was employed to account for multiple statistical comparisons; however, this was only carried out for the primary outcome of PFS and the secondary outcome of OS. None of the subsequent outcomes were statistically tested, including ORR. Similarly, pre-specified subgroup analyses of PFS and OS were not powered to test for differences in treatment effect between treatment groups nor were they controlled for multiplicity. Therefore, the results of all these analyses should be considered exploratory and hypothesis generating.

HRQOL was only assessed as an exploratory outcome, despite the importance of this endpoint to patients with ABC. There was a large amount of missing data from the analyses; for example, although baseline data were available from 99% of patients, end of treatment data were available for less than half of the original ITT population. A large amount of missing data introduces significant potential for confounding and selection bias in the analysis. For example, patients for whom assessment data were not available may be more likely to exhibit improved HRQOL, as they are presumably more likely to be responders and less likely to be experiencing adverse effects from study treatment. Additionally, with such a large number of missing patients, the balance in baseline characteristics between groups achieved through randomization may be lost; for example, a disproportionate number of patients in the tamoxifen background groups may remain in the study compared to the number intended.

There were more patients who had discontinued treatment in the placebo group than in the ribociclib group, and this resulted in a longer time of exposure to treatment with ribociclib than with placebo. This difference in exposure was unlikely to have biased the results for efficacy outcomes, as the reason for the difference in exposure was directly related to treatment failure with placebo. However, the increased exposure to ribociclib may have biased assessment of harms towards finding more harms with ribociclib.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

The primary efficacy analysis was performed on August 20, 2017, at which point median follow up of trial patients was 19.2 months. Efficacy outcomes of the MONALEESA-7 trial are summarized in Table 6.6.

Table 6.6: Efficacy Outcomes of the MONALEESA-7 trial

OUTCOMES	MONALEESA-7	
	Ribociclib N=335	Placebo N=337
PROGRESSION-FREE SURVIVAL		
INVESTIGATOR ASSESSMENT*		
Number of events - n (%)	131 (39)	187 (56)
-Progression	128 (38)	183 (54)
-Death[a]	3 (0.9)	4 (1)
HR (95% CI); p-value [b]	0.55 (0.44, 0.69); p<0.0001	
Median PFS, months (95% CI)	23.8 (19.2; NE)	13.0 (11.0, 16.4)
BIRC ASSESSMENT, N*	N=133	N=134
HR (95% CI) [b]	0.43 (0.29, 0.63)	
Median PFS, months (95% CI)	Not reached	11.1 (7.4, 16.9)
*Updated (exploratory) PFS***		
Median PFS, months (95% CI)-updated with November 30, 2018 cutoff	27.5 (Not reported)	13.8 (Not reported)
HR ratio (95% CI)	0.58 (0.48, 0.70)	
OVERALL SURVIVAL		
*1st interim analysis**		
Number of events – n (%)	43 (13)	46 (14)
2nd interim analysis		
Number of events – n (%)	83 (25)	109 (32)
Median OS, months (95% CI)	NE	40.9 (37.8, NE)
HR (95% CI); p-value [c]	0.71 (0.54, 0.95); p=0.00973	
OBJECTIVE RESPONSE		
*All patients**		
CR, n (%)	8 (2)	7 (2)
PR, n (%)	129 (39)	93 (28)
SD, n (%)	106 (32)	120 (36)
Non-CR/Non-PD, n (%)	60 (18)	53 (16)
PD, n (%)	24 (7)	52 (15)
Unknown, n (%)	8 (2)	12 (4)
ORR, n (%)	137 (41)	100 (30)
Patients with Measurable disease, N*	269 (80)	275 (82)
CR, n (%)	8 (3)	7 (3)
PR, n (%)	129 (48)	93 (34)
SD, n (%)	106 (39)	120 (44)
PD, n (%)	20 (7)	44 (16)
Unknown, n (%)	6 (2)	11 (4)
ORR, n (%)	137 (51)	100 (36)
TIME-TO-RESPONSE		
Median time-to-response*	Not reached	Not reached
DURATION OF RESPONSE		
Median DOR, months (95% CI)	21.3 (18.3, NE)	17.5 (12.0, NE)

TIME-TO-CHEMOTHERAPY		
Patients who had not yet received subsequent chemotherapy at 42 months, % (95% CI)**	65.8% (59.1, 71.7)	49.0% (41.1, 56.3)
HR (95% CI) for receipt of chemotherapy	0.60 (0.46, 0.77)	

Abbreviations: BIRC=blinded independent central review; CI = confidence interval; CR=complete response; DOR=duration of response; HR=hazard ratio; NE=not estimable; ORR=objective response rate; PD=progressive disease; PFS=progression-free survival; PR=partial response; SD – stable disease.

Notes:
[a] Death before progression.
[b] One-sided p-value obtained from log-rank test stratified by liver and/or lung metastases prior chemotherapy for advanced disease, and endocrine combination partner per interactive response technology (IRT). HR obtained from Cox proportional hazards model stratified by liver and/or lung metastases as per IRT.
[c] Log-rank test was stratified by lung and/or liver metastasis, prior chemotherapy for advanced disease, and endocrine combination partner per IRT. P-value is one-sided and was compared against a threshold of 0.00016 as determined by the Lan-DeMets (O'Brien-Fleming) alpha-spending function for an overall significance level of 0.025. HR obtained from Cox proportional hazards model stratified by lung and/or liver metastasis, prior chemotherapy for advanced disease, and endocrine combination partner as per IRT.

Median follow-up at data cut-off dates:
*August 20, 2017: 19.2 months
**November 30, 2018: 34.6 months

Sources: Tripathy 2018;[2] Im 2019;[4] FDA Clinical Review[5]

Primary Outcome - Progression-free Survival by Investigator Assessment

As of the data cut-off date (August 20, 2017), there were 318 progression events in total, with fewer progression events observed in the ribociclib group (n=131; 39% of patients) versus the placebo group (n=187; 56% of patients) for a statistically significant difference between groups (HR of 0.55 [95% CI: 0.44, 0.69]; Figure 6.3). Results from the BIRC assessment were consistent with that of the primary analysis (HR of 0.43 [95% CI: 0.29, 0.63]; Figure 6.3).

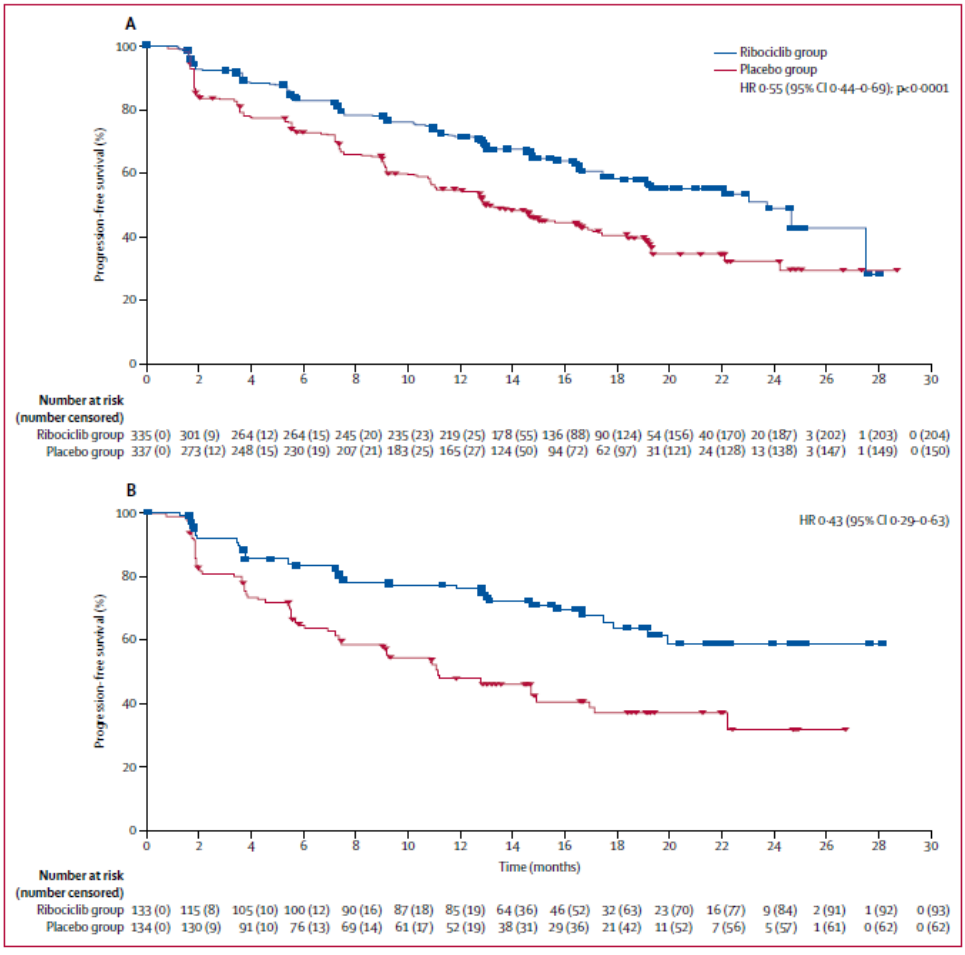
The median PFS by investigator assessment in the ribociclib group was 23.8 months (95% CI, 19.2, not reached) in the ribociclib group compared to 13.0 months in the placebo group (95% CI, 11.0, 16.4). The median PFS by BIRC assessment was not reached in the ribociclib group and was 11.1 months in the placebo group (95% CI: 7.4, 16.9).

With respect to subgroup analyses (Figure 6.4), in general, the treatment effect remained consistent across patient subgroups, with HRs ranging from 0.40 to 0.84, although the small sample sizes of some subgroups limit interpretation of the data. The treatment effect estimates for patients on a NSAI or tamoxifen were 0.57 (95% CI: 0.44, 0.74) and 0.59 (95% CI: 0.39, 0.88), respectively. There was an indication of PFS benefit in patients who had previously progressed >12 months after end of ET (HR of 0.75 [95% CI: 0.28, 2.02] versus those who had progressed on or within 12 months of ET (HR of 0.59 [95% CI: 0.40, 0.87]) or those with no prior ET (HR of 0.52 [95% CI: 0.38, 0.70]; however, the small sample size in the former subgroup (n=36) is a confounder when interpreting these data. As no tests for interaction were performed and these analyses were not controlled for multiplicity, the results should be considered exploratory and interpreted accordingly.

An updated (exploratory) analysis of PFS based on the November 30, 2018 data cut-off date (median follow-up of 34.6 months) was provided by the sponsor;[3] the median PFS at this time was 27.5 months in the ribociclib group and 13.8 months in the placebo group (CIs not provided). The updated HR was 0.58 (95% CI: 0.48, 0.70).[3]

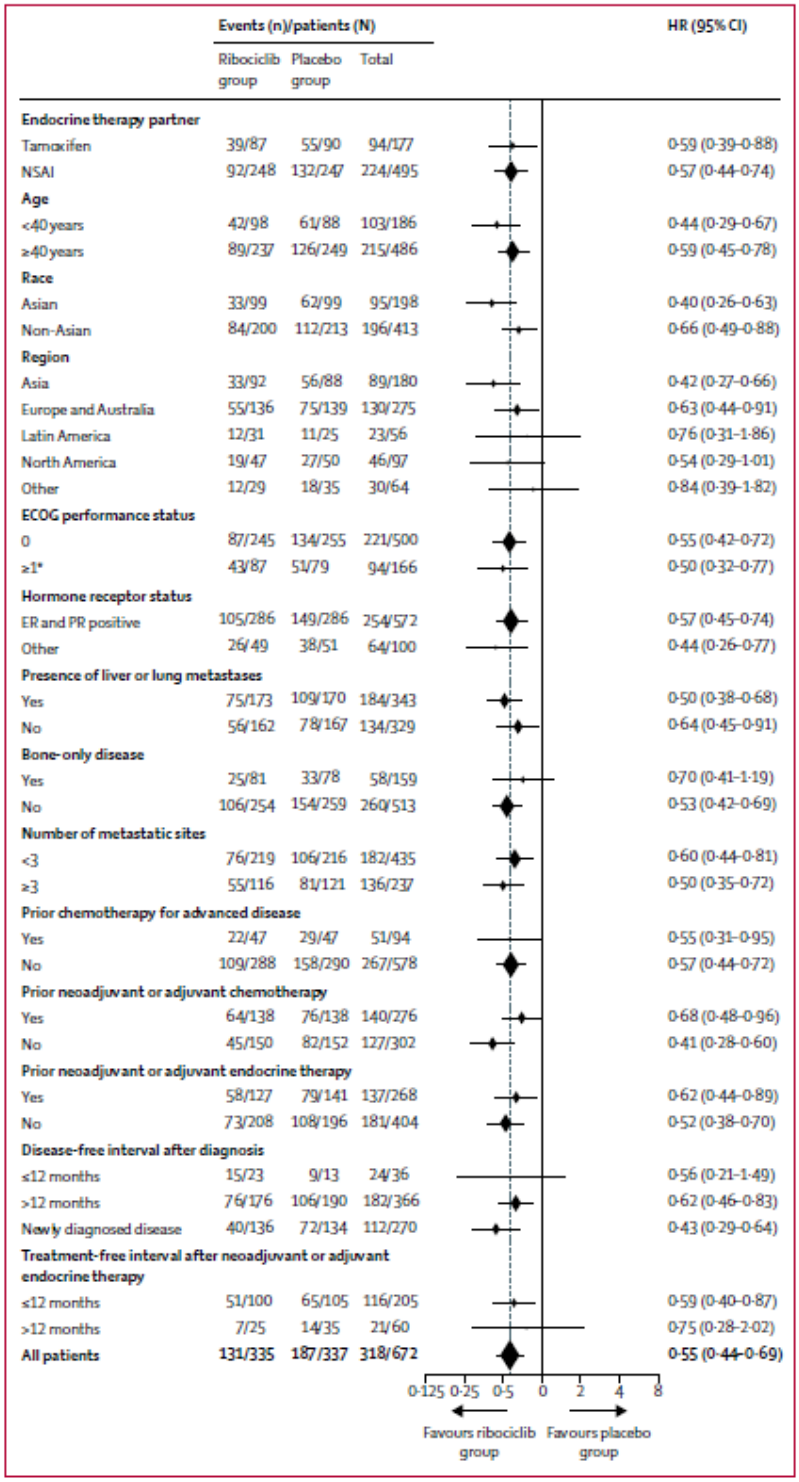
The outcomes of patients who moved on to subsequent therapy after discontinuing treatment in MONALEESA-7 was documented under the exploratory outcome PFS2. There were 38% (n=126) of patients in the ribociclib group and 48% (n=161) of patients in the placebo group who had a PFS2 event. The estimated percent of patients who were alive at 42 months and did not have disease progression while on second-line therapy was 55% in the ribociclib group and 38% in the placebo group for a HR for progression or death of 0.69 (95% CI: 0.55, 0.87).[4]

Figure 6.3: Kaplan-Meier analyses of PFS in MONALEESA-7 (A: PFS by investigator assessment; B: PFS by BIRC assessment)



Source: Reprinted from The Lancet Oncology, 19(7), Tripathy D et al., Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial, pg. 904-915, Copyright (2018), with permission from Elsevier.[2]

Figure 6.4: Subgroup analyses of PFS from the MONALEESA-7 trial.



Source: Reprinted from The Lancet Oncology, 19(7), Tripathy D et al., Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial, pg. 904-915, Copyright (2018), with permission from Elsevier.[2]

Key Secondary Outcome - Overall Survival

There was no statistically significant difference in OS as of the data cut-off date of the primary efficacy analysis of PFS (August 20, 2017), with 13% (n=43) of patients in the ribociclib group and 14% (n=46) of patients in the placebo group with an event of death at this time. However, by the time of the pre-planned second interim analysis,[4] after a median follow up of 34.6 months, there was a total of 192 deaths, with 25% (n=83) of patients in the ribociclib group and 32% (n=109) of patients in the placebo group with an event of death (HR of 0.71 [95% CI: 0.54, 0.95], p=0.00973). This was deemed to be a statistically significant reduction in the risk of death with ribociclib versus placebo, as the p-value crossed the pre-specified O'Brien-Fleming stopping boundary of p<0.01018. A pre-specified analysis of OS based on endocrine partner was performed (see Figure 6.5). In patients receiving a NSAI, 25% (n=61) of patients in the ribociclib group and 32% (n=80) of patients in the placebo group had died; while in those receiving tamoxifen, results were similar with 25% (n=22) of patients in the ribociclib group and 32% (n=29) of patients in the placebo group with an event of death. The HR for death in those receiving a NSAI was 0.70 (95% CI: 0.50, 0.98) and for those receiving tamoxifen was 0.79 (95% CI: 0.45, 1.38).

Other Secondary Outcomes

Objective Response

In the FAS (ITT) population, the ORR was 41% in the ribociclib group and 30% in the placebo group. A CR was observed in 2% of patients in each of the ribociclib and placebo groups, and a PR was observed in 39% versus 28% of patients in the ribociclib and placebo groups, respectively (refer to Table 6.6).

In patients with measurable disease at baseline (about 81% of the trial population), the ORR was 51% in the ribociclib group and 36% in the placebo group. A CR was observed in 3% of patients in each of the ribociclib and placebo groups; and a PR was observed in 48% and 34% of patients in the ribociclib and placebo groups, respectively (refer to Table 6.6).

Time-to-Objective Response

The median time-to objective response was not reached in either treatment group at the data cut-off date (refer to Table 6.6).

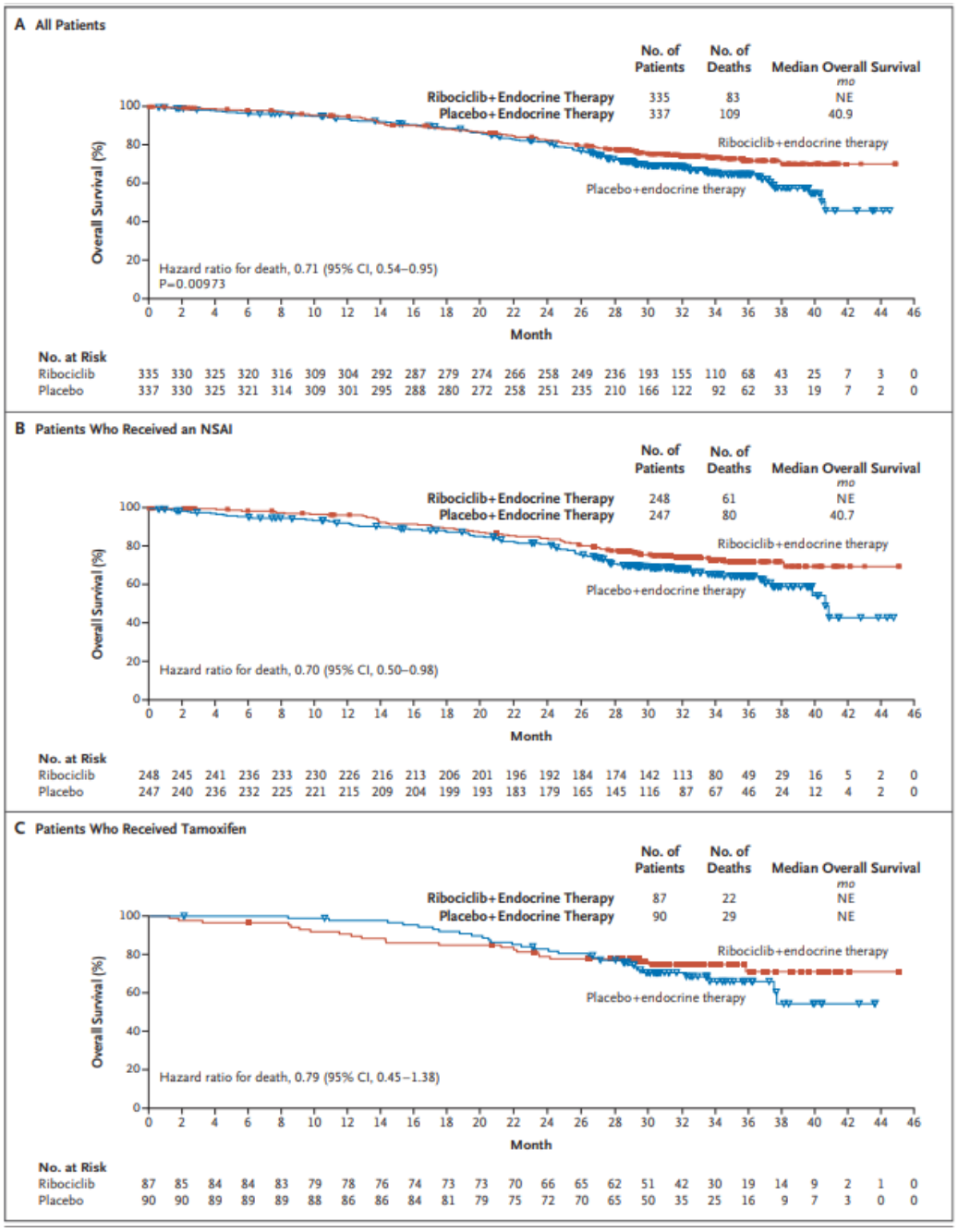
Duration of Response

The median DOR was 21.3 months (95% CI: 18.3, NE) in the ribociclib group and 17.5 months (95% CI, 12.0, NE) in the placebo group (refer to Table 6.6).

Time-to-Chemotherapy

The time-to-chemotherapy was an exploratory outcome of the trial. After 42 months, there were more ribociclib-treated patients, 65.8% (95% CI: 59.1, 71.7), who had not yet received subsequent chemotherapy compared to placebo at 49.0% (95% CI: 41.1, 56.3), for a HR for receipt of chemotherapy of 0.60 (95% CI: 0.46, 0.77).[4]

Figure 6.5: Kaplan-Meier analyses of overall survival based on second planned interim analysis (A: All patients; B: Patients who received NSAI; and C: Patients who received tamoxifen).



Source: From The New England Journal of Medicine, Im SA et al., Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer, 381(4), pg. 307-316. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. [4]

Health-related Quality of Life

HRQOL outcomes are summarized in Table 6.7. As previously mentioned, changes in HRQOL were expressed as the time-to-10% deterioration in subscales of the EORTC CLC30. A definitive 10% deterioration was a worsening in score by 10% or more when compared to baseline, with no later improvement above this threshold during the treatment period, or death due to any cause. Most patients (99%) had completed baseline assessments; however, end of treatment assessments were only completed for a proportion of the trial population (39% of patients in the ribociclib group and 53% in the placebo group).[6] The median time-to-10% definitive deterioration of global health status/QOL, the primary patient-reported outcome of interest, was not reached in the ribociclib group and was 21.2 months in the placebo group. The HR for time-to-deterioration in global health status/QOL favoured ribociclib and was 0.70 (95% CI: 0.53, 0.92). The other scales assessed showed similar results (Table 6.7). These results suggest that overall HRQOL is not worse with ribociclib when compared to ribociclib.

Table 6.7: Health-related quality of life outcomes of the MONALEESA-7 trial

HRQOL OUTCOMES	MONALEESA-7	
	Ribociclib N=335	Placebo N=337
Median follow-up in months	19.2	
HEALTH-RELATED QUALITY OF LIFE		
EORTC-QLQ-C30: GLOBAL HEALTH STATUS	N=332	N=332
Mean (SD) baseline	64.7 (22.3)	65.1 (22.6)
Mean (SD) change from baseline to EOT	N=129	N=179
	-4.4 (27.8)	-3.0 (23.4)
LSM change from baseline (95% CI)	-4.0 (-8.4, 0.4)	-2.4 (-6.4, 1.6)
Treatment difference (95% CI)	-1.6 (-6.6, 3.4)	
Median time to 10% definitive deterioration of EORTC QLQ-C30 global health status, months (95% CI)	Not reached (22.2, NE)	21.2 (15.4, 23.0)
HR (95% CI)	0.70 (0.53, 0.92)	
EORTC QLQ-C30 physical functioning scale	0.74 (0.54, 1.01)	
EORTC QLQ-C30 emotional functioning scale	0.72 (0.55, 0.95)	
EORTC QLQ-BR23 breast symptoms subscale	0.68 (0.45, 1.03)	
EORTC EQ-5D-5L, VAS scale	0.68 (0.51, 0.89)	

Abbreviations: CI = confidence interval; EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOT=end of treatment; EQ-5D-5L=EuroQol 5 Dimension 5 Level; HR=hazard ratio; LSM=least square mean; NE=not estimable; SD – standard deviation; VAS=visual analogue scale.

Sources: Tripathy 2018;[2] Im 2019;[4] FDA Clinical Review;[5] Checkpoint Responses[6]

Harms Outcomes

Adverse Events

Harms outcomes reported in the MONALEESA-7 trial are summarized in Table 6.8.

Adverse events of any grade were reported in 98% of patients in the ribociclib group and 94% of patients in the placebo group. Grade 3 and 4 events occurred in 63% and 14% of ribociclib patients, respectively, and 26% and 4% of placebo patients, respectively. The most common adverse event in the ribociclib group was neutropenia; grade 3 neutropenia occurred in 51% of patients treated with ribociclib compared to 3% of those who received placebo; and grade 4 neutropenia occurred in 10% versus 1% of patients, respectively.

Serious Adverse Events

Serious adverse events were reported in 18% of patients in the ribociclib group compared to 12% in the placebo group. There were no serious adverse events that occurred in more than 2% of patients in either group. Drug-induced injury was the most common serious adverse event occurring in 1.6% (n=4) of ribociclib and 0.4% (n=1) of placebo patients, followed by dyspnea, abdominal pain, and back pain, which each occurred in 1.2% (n=3) of ribociclib patients compared to 0.8% (n=2), 0%, and 0.4% (n=1) of placebo patients, respectively.[7] Abdominal pain and anemia (0.8%; n=2) were the serious adverse events that occurred with ribociclib but not with placebo.[7] There were two deaths in the ribociclib group that were not deemed related to study treatment: one patient died of an intracranial hemorrhage, and one patient died of wound hemorrhage.

Withdrawal due to Adverse Events

Withdrawals due to adverse events occurred in 4% of patients treated with ribociclib versus 3% of placebo patients. The most common reason for a withdrawal due to adverse event was ALT increased, occurring in 2% (n=6) of ribociclib patients and 0.8% (n=2) placebo patients.[7] Other adverse events leading to withdrawal included AST increased (2% [n=4] ribociclib versus <1% [n=2] placebo), drug-induced liver injury (1% [n=3] ribociclib versus <1% [n=1] placebo)[9] and QT prolongation (<1% [n=1] ribociclib versus <1% [n=2] placebo).

Notable Harms

Neutropenia was a notable harm and as mentioned previously, was the most common adverse event with ribociclib treatment. Febrile neutropenia occurred in 2% (n=7) of patients treated with ribociclib and 1% of patients treated with placebo (n=2). QT prolongation was another notable harm, and QTcF increases of >60 msec occurred in 10% of patients treated with ribociclib compared to 2% of patients in the placebo group. Breaking this down by endocrine background therapy, in the patients on tamoxifen, 16% (n=14) of ribociclib patients and 7% (n=6) placebo patients had increases in QTcF >60 msec, while for those on NSAI therapy, 7% (n=18) of ribociclib patients versus no placebo patients experienced an increase in QTcF >60 msec. There were no cases of torsades de pointes in the trial.

Hepatic events in the form of increased ALT was noted in 13% of patients in the ribociclib group compared to 9% of patients in the placebo group, and increased AST was noted in 13% versus 10% of patients, respectively. Fatigue occurred in similar numbers between groups (ribociclib: 24%; placebo: 25%).

An update on harms was provided with the updated OS analysis (median follow up of 34.6 months), and the authors noted that the adverse event profile remained consistent with that of the primary analysis.[4] The median duration of treatment exposure was approximately two years in the ribociclib group and one year in the placebo group. With respect to notable harms, grade 3 or 4 adverse events of neutropenia occurred in 63.5% of ribociclib versus 4.5% of placebo patients; hepatobiliary events occurred in 11% of ribociclib versus 6.8% of placebo patients, and QT prolongation occurred in 1.8% versus 1.2% of patients, respectively.[4]

Table 6.8: Summary of harms in the MONALEESA-7 trial

Harms Outcomes	MONALEESA-7					
	Ribociclib N=335			Placebo N=337		
ADVERSE EVENTS	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Patients with > 0 AEs, N (%)	72 (21)	210 (63)	47 (14)	217 (64)	88 (26)	12 (4)
Most common, 10% in any group						
Neutropenia	51 (15)	170 (51)	33 (10)	14 (4)	10 (3)	2 (1)
Hot flush	113 (34)	1 (<1)	0	113 (34)	0	0
Nausea	104 (31)	2 (1)	0	65 (19)	1 (<1)	0
Leucopenia	57 (17)	44 (13)	4 (1)	15 (4)	4 (1)	0
Arthralgia	97 (29)	3 (1)	0	89 (26)	3 (1)	0
Fatigue	75 (22)	4 (1)	0	83 (25)	0	0
Headache	77 (23)	0	0	79 (23)	3 (1)	0
Anemia	60 (18)	10 (3)	0	27 (8)	7 (2)	0
Diarrhea	63 (19)	5 (1)	0	62 (18)	1 (<1)	0
Vomiting	59 (18)	5 (1)	0	54 (16)	2 (1)	0
Alopecia	63 (19)	NA	NA	39 (12)	NA	NA
Back pain	56 (17)	4 (1)	0	61 (18)	4 (1)	0
Constipation	55 (16)	0	0	42 (12)	0	0
Pyrexia	49 (15)	2 (1)	0	27 (8)	0	0
Cough	50 (15)	0	NA	39 (12)	0	NA
Rash	43 (13)	1 (<1)	0	29 (9)	0	0
Increased ALT	25 (7)	18 (5)	0	20 (6)	5 (1)	0
Asthenia	41 (12)	2 (1)	0	41 (12)	0	0
Insomnia	42 (13)	0	0	46 (14)	0	0
Increased AST	28 (8)	12 (4)	0	26 (8)	4 (1)	0
Upper respiratory tract infection	36 (11)	2 (1)	0	29 (9)	1 (<1)	0
ECG QT prolonged	33 (10)	4 (1)	0	15 (4)	0	1 (<1)
Abdominal pain	32 (10)	2 (1)	1 (<1)	23 (7)	1 (<1)	0
Myalgia	34 (10)	0	0	37 (11)	0	0
Pain in extremity	34 (10)	0	0	31 (9)	3 (1)	0
Stomatitis	32 (10)	2 (1)	0	25 (7)	1 (<1)	0
Musculoskeletal pain	29 (9)	1 (<1)	0	35 (10)	1 (<1)	0
SERIOUS ADVERSE EVENTS						
Patients with > 0 SAEs, N (%)	60 (18)			39 (12)		
Suspected to be drug-related	15 (4)			6 (2)		
Most common, 1% any group						
Pleural effusion	2 (0.8)			4 (1.6)		
Abdominal pain	3 (1.2)			0		
Dyspnea	3 (1.2)			2 (0.8)		
Anemia						
Back pain	3 (1.2)			1 (0.4)		
Drug-induced liver injury	4 (1.6)			1 (0.4)		
WDAEs						
WDAEs, N (%)	12 (4)			10 (3)		
Most common WDAE that were suspected to be drug-related	2 (0.8)			0		
ALT increased	6 (2)			2 (0.8)		
AST increased	4 (2)			2 (<1)		
Drug-induced liver injury	3 (1)			1 (<1)		
QT prolongation	1 (<1)			2 (<1)		
DEATHS						
Number of deaths, N (%)	5 (1)			6 (2)		
Most common reasons						
Disease progression	3 (1)			6 (2)		
Hemorrhage intracranial	1 (<1)			0		

Harms Outcomes	MONALEESA-7					
	Ribociclib N=335			Placebo N=337		
ADVERSE EVENTS	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Wound hemorrhage	1 (<1)			0		
NOTABLE HARMS						
Neutropenia						
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Infections	156 (47)	13 (4)	0	124 (37)	4 (1)	0
Febrile neutropenia	7 (2)			2 (1)		
ECG abnormalities						
QTcF >480msec post baseline	23 (7)			4 (1)		
--QTcF >500 msec	5 (1)			1 (<1)		
QTcF increase >60msec	32 (10)			6 (2)		
--patients on background TAM	14 (16)			6 (7)		
--patients on background NSAI	18 (7)			0		

Abbreviations: AE=adverse events; ALT=Alanine Aminotransferase; AST=Aspartate aminotransferase; ECG=electrocardiogram; msec=milliseconds; NA=not applicable; NSAI=non-steroidal aromatase inhibitor; SAE=serious adverse events; TAM=tamoxifen; WDAE=withdrawal due to adverse events.

Sources: Tripathy 2018;[2] FDA Clinical Review[5]

6.4 Ongoing Trials

No additional ongoing trials evaluating ribociclib as initial ET in pre- or peri-menopausal women with HR-positive, HER2-negative ABC were identified.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of ribociclib combined with an AI (and a LHRH agonist) as initial endocrine-based treatment in pre- and peri-menopausal women with HR-positive, HER2-negative ABC:

- Critical Appraisal of a Sponsor-Submitted ITC

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

7.1 Critical Appraisal of Sponsor-Submitted Indirect Treatment Comparison

7.1.1 Objective

As the MONALEESA-7 trial did not include a comparison to an active relevant treatment comparator, the sponsor conducted an ITC to estimate the relative efficacy (PFS) and safety of ribociclib plus a NSAI versus selected treatments for pre- and peri-menopausal women with HR-positive, HER2-negative ABC who had not received prior therapy for advanced disease.[3] The objective of the ITC was to provide inputs for the pharmacoeconomic model in order to evaluate the cost-effectiveness and budget impact of ribociclib plus a NSAI for the indication under review. The ITC uses data from the MONALEESA-7 trial based on the most recent data cut-off date for PFS, which was November 30, 2018. At the request of pCODR, the Sponsor updated the ITC to include other relevant CDK 4/6 inhibitors including palbociclib and abemaciclib plus either an AI or fulvestrant.

7.1.2 Methods

Systematic Review

A systematic review of the literature was performed using electronic databases to identify relevant trials, however the specific databases searched were not reported. Databases were searched starting from 2007, when the test for HER2 was standardised, but the end date of the search was not specified. The search terms included HR-positive, advanced/metastatic breast cancer and terms for relevant interventions. This search was supplemented with reports identified through a more targeted review of the literature, that included PubMed and Google Scholar, conducted between July 2018 and August 2, 2018 and targeted RCTs in ABC that evaluated one or more of the treatments of interest (ribociclib, palbociclib, abemaciclib, fulvestrant, anastrozole, letrozole, exemestane, and tamoxifen) and reported information on PFS or OS. Only RCTs were considered. The targeted search was supplemented with searches of references of retrieved articles. Screening of titles and abstracts were conducted by one reviewer while a second reviewer verified all inclusion and 10% of exclusion decisions. Additional searches of PubMed were conducted for full text publications of any studies that were identified through conference abstracts. The total number of citations captured by the search strategies was not reported. The systematic review identified 30 unique studies (159 reports) and of these, three included ribociclib. Among the 30 studies, there were 21 (11 of which where only one treatment arm was relevant), and nine non-RCTs. It was noted that all RCTs had parallel assignment, and most were double-blind, multicentre, phase 3 trials.

The target population for the review was to correspond to the population enrolled in MONALEESA-7, namely pre- and peri-menopausal women with HR-positive, HER2-negative ABC who have had no prior ET for advanced disease. The primary outcome of interest was PFS and grade 3 or higher adverse events were also evaluated. OS and ORR were not considered as

outcomes as these endpoints were not required for the economic model, which utilized a Markov cohort approach.

The review focused on ribociclib plus a NSAI at the approved dose and regimen, until disease progression or unacceptable toxicity. Comparators were chosen based on published clinical trials, treatment guidelines, feedback from the sponsor, and availability of data to construct evidence networks. The comparators included the following:

- NSAI
- Palbociclib + fulvestrant 500 mg
- Abemaciclib + fulvestrant 500 mg
- Palbociclib + AI
- Abemaciclib + AI
- Tamoxifen
- Exemestane

Chemotherapy was not included in the list of comparators because its use was considered to typically be limited to patients with rapidly progressing and/or life-threatening disease.

Quality assessment of the included trials was performed using the York Centre for Reviews and Dissemination checklist for RCTs. Data extraction was performed by one reviewer and checked by a second reviewer, with discrepancies resolved by discussion with a third reviewer.

Methodology for ITC and Analysis of Adverse Events

The ITC was conducted using the Bucher method. As there were no multi-arm trials and no closed loops in the evidence network, and since analyses of Schoenfeld residuals suggested that the proportionality assumption was not violated for any of the comparisons in the network, the conduct of the ITC using the Bucher method with treatment effects expressed as HRs was considered appropriate. For direct comparisons involving more than one trial, pooled HRs were estimated using fixed or random effects meta-analysis.

The analysis of adverse events included all-cause grade 3 or higher events with an incidence ≥5% for any of the comparators of interest as these are the types of events associated with treatment costs or reductions in HRQOL. Data from the MONALEESA-7 trial was used to estimate the incidence of all-cause grade 3 or higher adverse events for ribociclib plus a NSAI, a NSAI alone, and tamoxifen. Similar data for other comparators were based on published information from the key publication of clinical trials. Where multiple trials were available, incidence was calculated by pooling the number of events across trial arms.

7.1.3 Findings

Systematic Review Results

A total of nine studies were included in the ITC (refer to Tables 7.1 and 7.2): MONALEESA-7, CONFIRM, EFECT, FALCON, MONARCH 2, MONARCH 3, PALOMA-2, PALOMA-3, and SoFEA. A list of excluded trials and reasons for their exclusion was not provided; however, it was noted that a confirmatory trial comparing fulvestrant 500 mg versus 250 mg was excluded because it was conducted exclusively in Chinese patients.

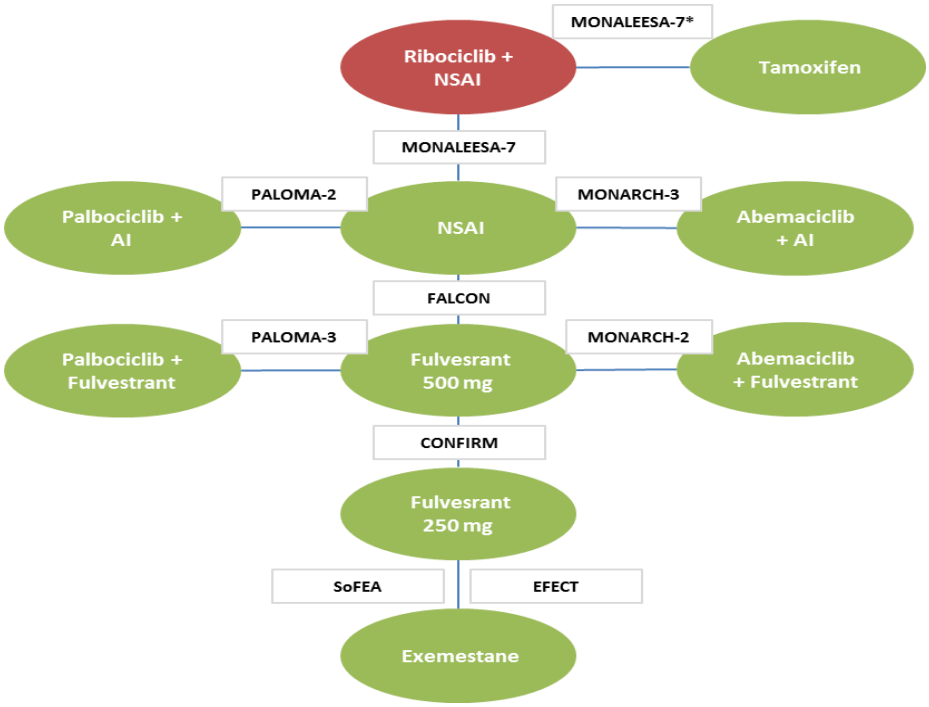
The authors noted that there were no trials of other CDK 4/6 inhibitors combined with a NSAI/AI that mirrored the population in MONALEESA-7 and that this limited comparisons between ribociclib and its closest CDK 4/6 comparators. With palbociclib and abemaciclib, the trials that included a pre- or peri-menopausal population combined these drugs with fulvestrant (MONARCH 2 and PALOMA-3);

thus, in order to focus on a pre- and peri-menopausal population, ribociclib plus a NSAI would have to be compared to these corresponding subgroups in the trials of abemaciclib or palbociclib plus fulvestrant. The evidence network is presented in Figure 7.1.

Although there were patients in MONALEESA-7 receiving tamoxifen as treatment for ABC, patients enrolled in the trial were randomized within strata defined by backbone ET (i.e., NSAI or tamoxifen). Accordingly, the comparison of ribociclib plus a NSAI with the placebo plus tamoxifen from this trial is not a randomized comparison. As such, the HR for PFS for tamoxifen versus ribociclib plus a NSAI was estimated using adjusted Cox proportional hazard regression model with covariates for demographic and disease characteristics.

Additionally, in two trials (SoFEA and EFECT), patients in the fulvestrant group received it at a dose of 500 mg intramuscularly on day 0, 250 mg on days 14 and 28, and 250 mg every 28 days thereafter. In the ITC, this dosing regimen was assumed to be equivalent in efficacy to fulvestrant 250 mg.

Figure 7.1. Evidence network for ITC



Source: ITC report submitted by sponsor [3]

Table 7.1: Key trial design features and baseline characteristics of patients included in the ITC

Trial/Source	Treatment	Control	% Pre-/Peri-Menopausal	Line of Treatment	Median PFS (months)		HR (95%CI)	Source/Notes
					Treatment	Control		
MONALEESA-7	Rib + NSAI + Gos	AI + Gos	100%	1L: 87% 2L: 13%	27.5	13.8	0.58 (0.48, 0.70)	Cox Proportional Hazards regression of patient level data from MONALEESA-7 (data on file)
MONALEESA-7	Rib + NSAI + Gos	Tam + Gos	100%	1L: 86% 2L: 14%	27.5	11.07	0.33 (0.23, 0.47)	Based on adjusted Cox PH regression of PFS for patients randomized to ribociclib + NSAI vs. PFS for patients randomized to placebo + tamoxifen with covariates for race, performance status, de novo disease, previous anticancer therapy, previous surgery, previous radiotherapy, number of disease sites, and location of metastases. PAI Analyses of MONALEESA-7 data (Novartis, data on file)
CONFIRM	Ful 500 mg	Ful 250 mg	0%	1L: 53% 2L: 47%	6.5	5.5	0.80 (0.68, 0.94)	HER2 status was not evaluated.
EFECT	Ful 250 mg	Exe	0%	1L: 13% 2L: 27% 3L: 60%	3.7	3.7	0.96 (0.82, 1.13)	Includes patients receiving both first- and second-line treatment for ABC, however, approximately 90% were second-line or subsequent.
FALCON	Ful 500 mg	AI	0%	1L 100%	16.6	13.8	0.80 (0.64, 1.00)	Includes only patients receiving first-line treatment for ABC. Less than 1% of patients were ER-, and <1% were HER2+.
MONARCH-2	Abe + Ful 500 mg	Ful 500 mg	100%*	1L: 59% 2L: 38% Unknown: 3%	16.4	9.3	0.42 (0.25, 0.70)	Trial included patients receiving both first- and second-line treatment for ABC, as well pre- and postmenopausal women. At least 40% of patients were receiving second-line treatment for ABC. Approximately 80% of patients were postmenopausal. HRs of PFS for abemaciclib vs. placebo, by line of therapy were not provided. NOTE: HR is specific to pre- and peri-menopausal subgroup, while the median PFS and line of therapy values are for the total population.
MONARCH-3	Abe + AI	AI	0%	1L: 100%	Not reached	14.7	0.54 (0.41, 0.72)	Includes only ET-sensitive patients receiving first-line treatment for ABC.
PALOMA-2	Pal + AI	AI	0%	1L: 100%	24.8	14.5	0.58 (0.46, 0.72)	Includes only ET-sensitive patients receiving first-line treatment for ABC.

Trial/Source	Treatment	Control	% Pre-/Peri-Menopausal	Line of Treatment	Median PFS (months)		HR (95%CI)	Source/Notes
					Treatment	Control		
PALOMA-3	Pal + Ful 500 mg	Ful 500 mg	100%*	1L: 25% 2L: 38% 3L: 28% 4L+: 9%	9.5	5.6	0.50 (0.29, 0.87)	Trial included patients receiving both first- and second-line treatment for ABC, as well pre- and postmenopausal women. Approximately 45% of patients were receiving second-line treatment for ABC; corresponding values for first-line and greater than second-line were ~25% and ~30%, respectively. Approximately 80% of patients were postmenopausal. HRs of PFS for placebo vs. placebo, by line of therapy were not provided in this paper. NOTE: The HR, median PFS, and line of therapy values reported here are specific to the pre- and peri-menopausal subgroup.
SoFEA	Ful 250 mg	Exe	0%	1L: 19% 2L: 82%	4.8	3.4	0.95 (0.79, 1.14)	Trial included patients receiving both first- and second-line treatment for ABC, however, at least 80% were second-line. Approximately 7% of patients were HER2+, while ~33% had unknown status.

Abbreviations: 1L=1st line; 2L=2nd line; 3L=3rd line; 4L=4th line; ABC=advanced breast cancer; Abe=abemaciclib; AI=aromatase inhibitor; CI=confidence interval; Exe=exemestane; Ful=fulvestrant; Gos=goserelin; HER2=human epidermal receptor; HR=hazard ratio; NSAI=non-steroidal aromatase inhibitor; Pal=palbociclib; PFS=progression-free survival; Rib=ribociclib; Tam=tamoxifen.

*HR was based on a subgroup of pre-/peri-menopausal patients. Among the ITT population, 21% and 18% of patients were pre-/peri-menopausal in PALOMA-3 and MONARCH-2, respectively.

Source: ITC report submitted by sponsor[3]

Table 7.2. Inclusion criteria for patient populations in trials of CDK4/6 inhibitors

Trial	CDK 4/6 Inhibitor	Backbone ET	Relapse ≤12 Months After Adjuvant Treatment With no Prior ET for Advanced Disease	Relapse >12 Months After Adjuvant Treatment With no Prior ET for Advanced Disease	De Novo ABC with No Prior ET	Prior Lines of ET in Advanced Setting	Menopause Status
MONALEESA-3	Rib	Ful	✓	✓	✓	1	Post
PALOMA-3	Pal	Ful	✓	X	X	≥1	Any
MONARCH-2	Abe	Ful	✓	X	X	1	Any
MONALEESA-2	Rib	AI	✓	✓	✓	0	Post
PALOMA-2	Pal	AI	✓	✓	✓	0	Post
MONARCH-3	Abe	AI	X	✓	✓	0	Post
MONALEESA-7	Rib	AI or Tam	✓	✓	✓	0	Pre/Peri

Abbreviations: ABC=Advanced breast cancer; Abe=abemaciclib; AI=aromatase inhibitor; CDK=cyclin dependent kinase; ET=endocrine therapy; Ful=fulvestrant; Gos=goserelin; Pal=palbociclib; Rib=ribociclib; Tam=tamoxifen

Source: ITC report submitted by sponsor[3]

ITC Results for PFS

In the ITC, there were no clear and consistent differences in PFS between ribociclib plus NSAI and other CDK 4/6 inhibitors plus NSAI, abemaciclib (HR of 0.94 [95% CI: 0.67, 1.32]) and palbociclib (HR of 1.01 [95% CI: 0.75, 1.35]). There was some evidence that when palbociclib (HR of 0.69 [95% CI: 0.37, 1.29]) or abemaciclib (HR of 0.57 [95% CI: 0.31, 1.04]) were combined with fulvestrant there was improved efficacy compared to ribociclib combined with a NSAI; however, these differences did not appear to be statistically significant, and interpretation of these results is greatly complicated by the use of different background ET.

Table 7.3: Summary of ITC results for PFS

Comparator	HR vs. NSAI (95% CI)	HR vs. Ribociclib + NSAI (95% CI)
Abemaciclib + fulvestrant 500 mg	0.33 (0.19, 0.58)	0.57 (0.31, 1.04)
Palbociclib + fulvestrant 500 mg	0.40 (0.22, 0.72)	0.69 (0.37, 1.29)
Abemaciclib + AI	0.54 (0.41, 0.72)	0.94 (0.67, 1.32)
Ribociclib + NSAI	0.58 (0.48, 0.70)	1.00 (n/a, n/a)
Palbociclib + AI	0.58 (0.46, 0.73)	1.01 (0.75, 1.35)
Fulvestrant	0.80 (0.64, 1.00)	1.38 (1.03, 1.86)
NSAI	1.00 (n/a, n/a)	1.73 (1.43, 2.10)
Exemestane	1.04 (0.77, 1.41)	1.80 (1.26, 2.58)
Tamoxifen	1.76 (1.16, 2.66)	3.05 (2.11, 4.40)

Abbreviations: AI=aromatase inhibitor; CI=confidence interval; HR=hazard ratio; n/a=not applicable; NSAI=non-steroidal aromatase inhibitor.

Source: ITC report submitted by sponsor[3]

Analysis of Adverse Events

The grade 3 (or higher) adverse events that appeared more frequent with the CDK 4/6 inhibitors was asymptomatic neutropenia. This occurred whether ribociclib was combined with a NSAI or fulvestrant. Among the CDK 4/6 inhibitors the incidence of neutropenia seemed to be highest with palbociclib (62%) and lowest with abemaciclib (27%).

Table 7.3: Adverse events grade 3 or higher

Grade 3+ Adverse Event, %	Rib/NSAI	NSAI	Tam	Exe	Rib/fulv	Pal/fulv	Abe/fulv	Fulv
Abnormal LFT	0%	0.4%	0%	0%	0%	0%	0%	0%
Anemia	2.4%	1.2%	3.3%	0%	3.1%	2.9%	7.2%	1.7%
Decreased leukocyte count	6.0%	0.4%	1.1%	0%	14.1%	25.9%	8.8%	0.3%
Diarrhea	2.0%	0%	1.1%	0%	0.6%	0%	13.4%	0.5%
Fatigue	0.8%	0%	0%	1%	1.7%	2.9%	2.7%	0.7%
Hypertension	2.4%	2.8%	2.2%	0%	0%	0%	0%	0%
Increased ALT	4.8%	1.2%	2.2%	2%	0%	0%	4.1%	1.8%
Increased GGT	0.8%	3.6%	3.3%	7%	0%	0%	0%	0%
Infection	3.6%	1.2%	1.1%	0%	0%	1.8%	0%	2.9%
Neutropenia	0%	1.6%	3.3%	0%	53.4%	61.7%	26.5%	0.8%
Neutropenic asymptomatic	45.2%	0%	0%	0%	0%	0%	0%	0%
Pain	0%	0%	0%	0%	0%	0%	0%	0%
Pneumonia	0.4%	0.4%	0%	0%	0%	0%	0%	0%
PNNs	0%	0%	0%	0%	0%	0%	0%	0%
PPE syndrome	0.8%	0%	0%	0%	0%	0.4%	0.5%	0%
Stomatitis	0%	0.4%	0%	0%	0%	0%	0%	0%

Abbreviations: Abe/fulv=abemaciclib plus fulvestrant; ALT=alanine aminotransferase; Exe=exemestane; Fulv=fulvestrant; GGT=gamma glutamyl transferase; LFT=liver function test; NSAI=non-steroidal aromatase inhibitor; Pal/fulv=palbociclib plus fulvestrant; Rib=ribociclib; Rib/fulv=ribociclib plus fulvestrant; Tam=tamoxifen

Source: ITC report submitted by sponsor[3]

Conclusions of ITC

The authors noted the limitations of the ITC, and in this context concluded that ribociclib plus a NSAI may be an effective combination for pre- and peri-menopausal women with HR-positive, HER2-negative ABC who have not received prior treatment for ABC.

Critical Appraisal

The quality of the submitted ITC was assessed according to the ISPOR (International Society for Pharmacoeconomics and Outcomes Research) Task Force on Indirect Treatment Comparisons Questionnaire.[49] Details of the critical appraisal are presented in Table 7.4.

The significant heterogeneity between the trials included in the ITC is a major limitation, and therefore the results of the analyses should be interpreted with caution. There were no data suggesting a clear and consistent difference in efficacy between ribociclib and other CDK 4/6 inhibitors, and when combined with fulvestrant. These comparisons are limited by important differences between the included trials. The key difference being that in the trials where CDK inhibitors were combined with an AI/NSAI, which included PALOMA-2 (palbociclib) and

MONARCH-3 (abemaciclib), MONALEESA-7 was conducted in pre- and peri-menopausal patients while the trials of abemaciclib and palbociclib were conducted exclusively in post-menopausal patients. Additionally, some of the patients in MONALEESA-7 were ET-resistant (relapsed within 12 months of completing [neo]adjuvant ET), while patients in MONARCH-3 were required to be ET-sensitive (relapsed >12 months after completion of [neo]adjuvant ET). The baseline characteristics of patient populations in the included trials were not adequately described, however, there were notable differences across the trials related to menopausal status, endocrine partner, disease-free interval, inclusion of de novo ABC patients, and line of therapy. Information on other important patient and trial characteristics (i.e., patient demographics, study locations, PFS definitions and assessment schedule, median follow-up time) was not reported. Due to a lack of information, it is not possible to determine whether other important baseline characteristics also differed between the trials. In addition, the results of the quality assessment of individual trials were not reported and thus, the quality of included trials cannot be easily determined.

The ITC focused on PFS as the main efficacy outcome but other key outcomes such as OS, objective response, and patient-reported outcomes were not included in the analysis. It is unclear whether reported results were based on fixed or random effects models of analysis. No formal statistical comparison of adverse events was performed between comparators; however, the naïve comparison performed suggested the CDK inhibitors, as a group, appear to carry a higher risk of various cytopenias, including neutropenia, when compared to other therapies.

Overall, the ITC results should be interpreted with caution given the significant clinical heterogeneity across trials that could impact their comparability to the MONALEESA-7 trial and produce biased estimates of relative treatment effect.

Table 7.4: ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis[†]

ISPOR Questions	Details and Comments[‡]
1. Is the population relevant?	Yes. Pre- and peri-menopausal women with HR-positive, HER2-negative ABC.
2. Are any critical interventions missing?	Yes. Chemotherapy was not included as a comparator. The authors stated that this was because it is typically reserved for patients with rapid progression or with life-threatening metastases. In response to a request from pCODR, the sponsor added CDK 4/6 inhibitor combination therapies that included palbociclib and abemaciclib each combined with an AI or fulvestrant.
3. Are any relevant outcomes missing?	**Yes. The ITC focused on PFS, which is a priority efficacy outcome. However, other outcomes including OS, objective response, and HRQOL were not assessed. A naïve comparison of adverse events was included.**
4. Is the context (e.g., settings and circumstances) applicable to your population?	Unclear. Details on trial and patient population characteristics (e.g., patient demographics, study locations, PFS definitions and assessment schedule, median follow-up time) of the included trials were missing from the ITC report.
5. Did the researchers attempt to identify and include all relevant RCTs?	Unclear. A literature search of electronic databases was performed though the specific databases searched were not reported. A supplemental targeted search was also performed but it is unclear why this second search was needed.
6. Do the trials for the interventions of interest form one connected	Yes.

ISPOR Questions	Details and Comments‡
network of randomized controlled trials?	
7. Is it apparent that poor quality studies were included thereby leading to bias?	Unclear. Details regarding study design were not reported though RCTs were sought. The results of the quality assessment of individual trials were not reported.
8. Is it likely that bias was introduced by selective reporting of outcomes in the studies?	Unclear. A list of the trials excluded from the ITC was not provided; thus, it is not known whether any trials were excluded on the basis of not reporting outcomes of interest.
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. There were important differences in baseline characteristics between included trials, most notably the number of patients who were post-menopausal versus pre-/peri-menopausal, and in the prior experience with ET. Only a select number of baseline characteristics were reported for the individual trials; thus, it is not possible to determine whether other important baseline characteristics also differed between the 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?	Yes. The authors noted the major differences in patient populations prior to comparing individual trial results.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**No, not for harms. Naïve comparisons of adverse events data were performed. The authors acknowledged the limitations of this type of analysis; however, they stated that this approach was chosen due to the small number of events (many were zero) for many of the adverse events of interest. For the analysis of PFS, the comparison of ribociclib plus NSAI versus tamoxifen from the MONALEESA-7 trial was not a randomized comparison and therefore effect estimates were based on a Cox regression analysis.**
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?	N/A. There were no closed loops in the network.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	N/A
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 with the analysis?	N/A.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	No. The authors stated that fixed or random effects models may be used but did not state the type(s) of analyses actually performed.
16. If a random effects model was used, were assumptions about	Unknown.

ISPOR Questions	Details and Comments‡
heterogeneity explored or discussed?	
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**No.**
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes. A figure illustrating the evidence network was provided, and this identified the specific trials contributing to each comparison in the network.
19. Are the individual study results reported?	Yes, treatment effect estimates for PFS were reported for each of the included trials.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	N/A
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes. Measures of uncertainty (95% CI) accompanied PFS treatment effect estimates.
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. The conclusions were qualified with the limitations of the analysis, which suggested exercising caution in drawing conclusions due to concerns over heterogeneity between the included trials.
25. Were there any potential conflicts of interest?	**Yes. No conflicts of interest were declared; however, the ITC was performed by a company contracted by the sponsor.**
26. If yes, were steps taken to address these?	**No. The ITC report does not appear to be peer-reviewed.**

† Adapted from Jansen 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.
‡Bolded comments are considered a weakness of the ITC.

7.1.4 Summary

Since the MONALEESA-7 trial did not include a comparison to an active relevant treatment comparator, the sponsor conducted an ITC to estimate the relative efficacy (PFS) and safety of ribociclib plus a NSAI versus selected treatments for pre- and peri-menopausal women with HR-positive, HER2-negative ABC who have not received prior ET for ABC. The ITC was used to inform the pharmacoeconomic model supporting the reimbursement request.

Eligible trials were identified from a systematic review of electronic databases performed in April 2018 seeking RCTs and was supplemented with studies identified through a more targeted review of the literature. The ITC of PFS was conducted using the Bucher method, while adverse events were evaluated using an unanchored (naïve) comparison. After a request from pCODR, the ITC was updated to include other CDK 4/6 inhibitors combined with AI or fulvestrant as relevant comparators. The ITC

uses the most recent data cut-off date for PFS from the MONALEESA-7 trial, which was November 30, 2018.

The ITC included nine trials; however, there were no trials of CDK 4/6 inhibitors whose populations mirrored that of the MONALEESA-7 trial, thus limiting the conclusions that can be drawn from the analysis. The only available comparisons were based on patient subgroup data, and these suggested no clear differences in efficacy between ribociclib and other CDK 4/6 inhibitors in this population. The ITC results showed that there was improved efficacy for ribociclib combined with a NSAI when compared with palbociclib plus fulvestrant (HR of 0.69; 95% CI: 0.37, 1.29) or abemaciclib plus fulvestrant (HR of 0.57; 95% CI: 0.31, 1.04); however, these differences were not statistically significant. The pCODR Methods Team considered the significant heterogeneity in patient populations among the included trials as a major limitation of the ITC; there were notable differences across the trials related to menopausal status, endocrine partner, disease-free interval, inclusion of de novo ABC patients, and line of therapy, as well as missing information on other important patient and trial characteristics (i.e., patient demographics, study locations, PFS definitions and assessment schedule, median follow-up time). Overall, the ITC results should be interpreted with caution given the significant clinical heterogeneity across trials that could impact their comparability to the MONALEESA-7 trial and produce biased estimates of relative treatment effect.

8 COMPARISON WITH OTHER LITERATURE

No comparisons to other literature were identified.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Breast CGP 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 in pre- and peri-menopausal ABC. 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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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 additional information regarding the patient eligibility criteria of the MONALEESA-7 trial, as it pertains to prior (neo)adjuvant ET, was added to the Final Clinical Guidance Report.

The Breast CGP 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 AND DETAILED METHODOLOGY

1. Literature search via Ovid platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** July 2019**, Embase** 1974 to 2019 September 03**, Ovid MEDLINE(R) ALL** 1946 to September 03, 2019

#	Search Strategy	Results
1	(kisqali* or ribociclib* or kryxana* or LEE-011 or LEE-011A or LEE011 or LEE011A or LEE011-BBA or LEE011BBA or TK8ERE8P56 or BG7HLX2919 or L01XE).ti,ab,ot,kf,kw,hw,rn,nm.	1434
2	exp Breast Neoplasms/	798310
3	exp Breast/ or (breast* or mammar* or nipple* or lobular*).ti,ab,kw,kf.	1206313
4	(neoplasm* or neoplastic or malignan* or carcinoma* or cancer* or carcinoid* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or tumor* or tumour* or sarcoma* or metasta*).ti,ab,kw,kf.	7743185
5	3 and 4	916423
6	(mBC or m-BC or LABC).ti,ab,kf,kw.	21807
7	2 or 5 or 6	1070147
8	1 and 7	1036
9	8 use cctr	147
10	8 use medall	199
11	9 or 10	346
12	*ribociclib/	267
13	(kisqali* or ribociclib* or kryxana* or LEE-011 or LEE-011A or LEE011 or LEE011A or LEE011-BBA or LEE011BBA or L01XE).ti,ab,kw,dq.	1029
14	12 or 13	1044
15	exp Breast Tumor/	798310
16	exp Breast/ or (breast* or mammar* or nipple* or lobular*).ti,ab,kw.	1205998
17	(neoplasm* or neoplastic or malignan* or carcinoma* or cancer* or carcinoid* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or tumor* or tumour* or sarcoma* or metasta*).ti,ab,kw.	7701666
18	16 and 17	914307
19	(mBC or m-BC or LABC).ti,ab,kw.	21784

20	15 or 18 or 19	1069422
21	14 and 20	793
22	21 use oemezd	465
23	22 not conference abstract.pt.	233
24	11 or 23	579
25	remove duplicates from 24	378
26	22 and conference abstract.pt.	232
27	limit 26 to yr="2014 -Current"	230
28	25 or 27	608
29	limit 28 to english language	563

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items found
#10	Search **#8 AND #9**	10
#9	Search **publisher[sb]**	406840
#8	Search **#1 AND #7**	200
#7	Search **#2 OR #5 OR #6**	416214
#6	Search **mBC[tiab] OR m-BC[tiab] OR LABC[tiab]**	7233
#5	Search **#3 AND #4**	365734
#4	Search **neoplasm*[tiab] OR neoplastic[tiab] OR malignan*[tiab] OR carcinoma*[tiab] OR cancer[tiab] OR cancers[tiab] OR carcinoid*[tiab] OR carcinogen*[tiab] OR adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour[tiab] OR tumours[tiab] OR sarcoma*[tiab] OR metasta*[tiab]**	3271506
#3	Search **Breast[MeSH] OR breast*[tiab] OR mammar*[tiab] OR nipple*[tiab] OR lobular*[tiab]**	493785
#2	Search **Breast Neoplasms[MeSH]**	280329
#1	Search **kisqali*[tiab] OR ribociclib*[tiab] OR kryxana*[tiab] OR LEE-011[tiab] OR LEE-011A[tiab] OR LEE011[tiab] OR LEE011A[tiab] OR LEE011-BBA[tiab] OR LEE011BBA[tiab] OR TK8ERE8P56[rn] OR BG7HLX2919[rn] OR L01XE[tiab] OR ribociclib[supplementary concept]**	273

3. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

4. Grey literature search via:

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

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

Search: Kisqali/ribociclib, breast cancer

Select international agencies including:

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

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

Search: Kisqali/ribociclib, breast cancer

Conference abstracts:

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

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

Search: Kisqali/ribociclib, breast cancer — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the PRESS (Peer Review of Electronic Search Strategies) checklist (https://www.cadth.ca/resources/finding-evidence/press).[50]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) 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) and breast cancer.

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 19, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[51]

Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's 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) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented through contacts with the CADTH Clinical Guidance Panel (CGP). As well, 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.

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 CGP 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.

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