CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ribociclib (Kisqali) plus Fulvestrant for Advanced or Metastatic Breast Cancer

April 22, 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 plus fulvestrant for 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 plus fulvestrant for 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; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on ribociclib plus fulvestrant for ABC, a summary of submitted Provincial Advisory Group Input on ribociclib plus fulvestrant for ABC, and a summary of submitted Registered Clinician Input on ribociclib plus fulvestrant for ABC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The reimbursement request is ribociclib (KISQALI) in combination with fulvestrant for the treatment of post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative ABC, as initial therapy or following disease progression. 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] When co-administered with ribociclib, the recommended dose of fulvestrant is 500 mg administered intramuscularly on days 1, 15 and 29, an once monthly thereafter. A duration of treatment is not specified. The product monograph for fulvestrant 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, sponsor-funded, randomized controlled trial (RCT), MONALEESA-3, was included in the systematic review.[2] MONALEESA-3 randomized 726 post-menopausal patients with HR-positive, HER2-negative ABC from 174 sites in 30 countries, including Canada (12 patients).[3] A total of 726 patients were randomized in a 2:1 manner to either ribociclib (n=484) or placebo (n=242), both on a background of fulvestrant. Patients in the intervention group received ribociclib 600 mg orally once daily for days 1 to 21 of a 28-day cycle and fulvestrant 500 mg intramuscularly on day 1 of each cycle with an

additional injection on day 15 of cycle 1. Patients in the control group received placebo matched to ribociclib. Treatment continued until patients experienced disease progression, unacceptable toxicity, death, or discontinuation for any other reason.

Enrolled patients had a median of 63 years of age, all were female, and 85% were Caucasian. About two thirds (65%) of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, while the remainder had a status of 1. At trial entry, almost all patients (99%) had stage IV disease. Approximately 60% of patients had visceral metastases and approximately 21% had bone metastases only. The majority of patients (78%) had more than 12 months elapse since their initial diagnosis of primary breast cancer. Approximately 19% of patients had de novo disease. The majority of patients had prior endocrine therapy (ET); in the ribociclib group approximately 49% of patients received up to one prior line of ET compared to 45% in the placebo group. Approximately 49% of patients were treatment naïve for ABC in the ribociclib group compared to 53% in the placebo group.

Randomization was stratified by the presence of lung or liver metastases (yes/no), and previous ET, and patients were classified as follows:

- Group A - first-line treatment (endocrine sensitive): patients whose disease relapsed more than12 months after completion of (neo)adjuvant ET with no subsequent treatment for ABC, or patients with do novo ABC (no prior exposure to ET);
- Group B - second-line treatment or early relapse (endocrine resistant): patients who received up to one line of treatment for ABC, and
    - i) whose disease relapsed on or within 12 months from completion of (neo)adjuvant ET, with no subsequent treatment for ABC, or
    - ii) relapsed more than 12 months after completion of (neo)adjuvant ET, and progressed on or after subsequent ET for ABC, or
    - iii) had ABC at time of diagnosis that progressed on or after ET for ABC with no prior (neo)adjuvant therapy for early disease.

A summary of key outcomes from the MONALEESA-3 trial is provided in Table 1.1.

Table 1.1: Highlights of Key Outcomes in the MONALEESA-3 trial

Outcomes	MONALEESA-3	
	Ribociclib N=483	Placebo N=241
PROGRESSION FREE SURVIVAL – INVESTIGATOR ASSESSMENT		
*Primary efficacy analysis**		
Median PFS, months (95% CI)	20.5 (18.5 to 23.5)	12.8 (10.9 to 16.3)
HR (95% CI); p-value [a]	0.59 (0.48, 0.73); p<0.001	
BIRC assessment	N=193	N=97
HR (95% CI) [a]	0.49 (0.35 to 0.70)	
*Updated (exploratory) PFS***		
Median PFS, months (95% CI)	20.6 (not reported)	12.8 (not reported)
HR (95% CI)[a]	0.59 (0.49, 0.71)	
OVERALL SURVIVAL		
*1st interim analysis**		
Number of events – n (%)	70 (14.5)	50 (20.7)
HR (95% CI); p-value	0.67 (0.47, 0.96); p=0.015	
*2nd interim analysis***		
Number of events – n (%)	167 (34.5)	108 (44.6)
Median OS (95% CI)	Not reached	40.0 (37.0, NE)
HR (95% CI); p-value [b]	0.72 (0.57, 0.92); p=0.00455	
OVERALL RESPONSE		
*All patients**		
CR	8 (2)	0
PR	149 (31)	52 (22)
SD	161 (33)	83 (34)
Non-CR/Non-PD	88 (18)	54 (22)
PD	48 (10)	40 (17)
Unknown	30 (6)	13 (5)
ORR, N (%) [95% CI]	157 (32) [28 to 37]	52 (22) [16 to 27]
TIME-TO-RESPONSE		
Median time-to-response*	Not reached	Not reached
DURATION OF RESPONSE		
Median DOR*	Not reached	Not reached
HEALTH-RELATED QUALITY OF LIFE*		
Median time-to-10% deterioration in global health status/QoL scale of EORTC QLQ-C30	Not reached	19.4 months
HR (95% CI)	0.80 (0.60, 1.05)	
Time-to-10% deterioration in BPI-SF worst pain HR (95% CI)	0.81 (0.58, 1.13)	
Median time to 10% deterioration in physical functioning scale score of EORTC QLQ-C30 HR (95% CI)	Numerical results not reported, but 'no meaningful difference observed'	
Median time to 10% deterioration in emotional functioning scale score of EORTC QLQ-C30 HR (95% CI)	Numerical results not reported, but 'no meaningful difference observed'	
Median time to 10% deterioration in social functioning scale score of EORTC QLQ-C30 HR (95% CI)	Numerical results not reported, but 'no meaningful difference observed'	
Time-to-10% deterioration in BPI-SF pain severity index HR (95% CI)	0.81 (0.60, 1.11)	
Time-to 10%-deterioration in BPI-SF pain interference index HR (95% CI)	0.87 (0.63, 1.21)	
Time-to 10%-deterioration EQ-5D-5L VAS HR (95% CI)	0.87 (0.66, 1.16)	
HARMS*		

Outcomes	MONALEESA-3	
	Ribociclib N=483	Placebo N=241
Patients with a serious adverse event, n (%)	138 (29)	40 (17)
Withdrawals due to adverse event, n (%)	83 (17)	15 (6)
Deaths, n (%)	13 (3)	8 (3)
Notable harms		
Neutropenia	336 (70)	5 (2)

Abbreviations: BIRC=blinded independent radiology committee; BPI-SF=Brief Pain Inventory-short form; CI = confidence interval; CR=complete response; EORTC QLQ-C30= European Organization for the Research and Treatment of Cancer, Quality of Life Questionnaire; HR=hazard ratio; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PD=progressive disease; PR=partial response; QoL=quality of life; SD=stable disease; VAS=visual analogue scale.

Notes:
[a] One-sided p-value obtained from stratified log-rank test. Hazard ratio obtained from Cox proportional hazards model stratified by liver and/or lung metastases and previous endocrine therapy as per interactive response technology (IRT).

[b] 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 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:
*November 3, 2017: 20.4 months
**June 3, 2019: 39.4 months

Source: Slamon 2018;[2] Slamon 2020;[4] FDA Clinical Review[5]

Primary Outcome – Investigator Assessed PFS

The primary outcome was investigator-assessed progression-free survival (PFS), and the primary efficacy analysis of PFS was to be carried out once 125 PFS events had occurred in treatment naïve patients or after 364 events in total across both treatment groups, whichever came later.

As of the primary efficacy analysis data cut-off date of November 3, 2017 (median follow-up of 20.4 months), there were 361 progression events across the trial, and fewer progression events in the ribociclib group (n=210; 43% of patients) versus the placebo group (n=151; 62% of patients) for a statistically significant difference between treatment groups (hazard ratio [HR] of 0.59 [95% confidence interval [CI]: 0.48, 0.73]; p<0.0001). The median PFS with ribociclib was 20.5 months (95% CI: 18.5, 23.5) and with placebo was 12.8 months (95% CI: 10.9, 16.3). The treatment effect remained consistent across various patient subgroups, including prior ET (treatment naïve: HR of 0.58 [95% CI: 0.42, 0.80]; and up to one line of ET: HR of 0.57 [95% CI: 0.42-0.74]), prior use of tamoxifen (HR of 0.62 [95% CI: 0.44, 0.87]) and prior use of AI (HR of 0.67 [95% CI:0.51, 0.89]). Findings from the blinded independent radiology committee (BIRC) assessment of PFS were consistent with those of the investigator assessment with respect to treatment difference between groups.

An updated exploratory analysis of PFS was performed at the data cut-off date of June 3, 2019 after a median follow-up of 39.4 months and was consistent with the

primary efficacy analysis; the median PFS was 20.6 months in the ribociclib group and 12.8 months in the placebo group (HR of 0.59 [95% CI: 0.49, 0.71]).[4]

Key Secondary Outcome – Overall Survival

Overall survival (OS) was a key secondary outcome that was part of hierarchical testing. Three interim analyses were planned, one at the time of the PFS assessment (161 deaths anticipated at this time), the second after 263 deaths, and the third after 351 deaths.

There was no statistically significant difference in OS as of the primary analysis data cut-off date, with 15% (n=70) of patients in the ribociclib group and 21% (n=50) of patients in placebo with an event of death at this time point. However, by the time of the pre-planned second interim analysis (June 3, 2019), at a median follow up of 39.4 months, there was a total of 275 deaths, 35% (n=167) of patients had an event of death in the ribociclib group compared to 45% (n=108) of patients in the placebo group, and this difference was statistically significant (HR of 0.72 [95% CI: 0.57, 0.92]; p=0.00455).[4] The median OS was not reached in the ribociclib group and was 40.0 months (95% CI: 37.0, not estimable) in the placebo group. Pre-specified subgroup analyses of OS suggested that the treatment effect remained consistent across various subgroups, including analyses based on line of therapy (first-line: HR of 0.70 [95% CI: 0.48, 1.02] and early relapse or second-line: HR of 0.73 [95% CI: 0.53, 1.00]).[4]

Other Secondary Outcomes

In the full analysis set (all patients; intent-to-treat), the overall response rate (ORR) was 32% (95% CI: 28%, 37%) in the ribociclib group and 22% (95% CI: 16%, 27%) in the placebo group. Complete responses (CR) occurred in 2% (n=8) of ribociclib patients and no placebo patients, and partial responses (PR) occurred in 31% (n=149) of ribociclib patients and 22% (n=52) of placebo patients. For the results of other response outcomes refer to Table 1.1.

Health-related quality of life (HRQOL) was assessed using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), the EuroQoL 5-Dimensions 5-Level (EQ-5D-5L) questionnaire, and the Brief Pain Inventory Short Form (BPI-SF). Baseline assessments for the EORTC-QLQ-C30 were obtained from 93% of patients in MONALEESA-3; however, by the time end of treatment assessments were performed, data were only available from 41% of patients.[6] Changes in HRQOL were expressed as time-to-10% deterioration in the global health status/QOL subscale of the EORTC QLQ-C30, which was the primary patient-reported outcome of interest. A definitive 10% deterioration was defined as a worsening of 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. The HR for deterioration in global health status/QOL was 0.80 (95% CI: 0.60, 1.05). Similarly, there were no differences between the groups in any of the other subscales assessed.

At the time of the primary efficacy analysis the median duration of treatment exposure in the ribociclib group was 15.8 months compared to 12 months in the placebo group. Adverse events (all grades) occurred in 99% of patients in the ribociclib group and 96% of placebo. Grade 3 or 4 adverse events occurred in 78% of patients treated with ribociclib and 30% of patients treated with placebo; the most common adverse event was neutropenia, which occurred in 70% of ribociclib-treated and 2% of placebo-treated patients. Grade 4 neutropenia occurred in 7% of ribociclib patients versus none with placebo. Other cytopenias also occurred with

greater frequency in patients treated with ribociclib compared to placebo patients and including anemia (17% versus 5%) and leukopenia (28% versus 2%). Adverse events where there was a 10% difference between groups included nausea (45% versus 28%) and vomiting (27% versus 13%), constipation (25% versus 12%), and alopecia (19% versus 5%). QT prolongation occurred in 7% of patients in the ribociclib group versus <1% of patients in the placebo group. There were no cases of torsades de pointes.

Adverse events were the most common reason for dose reduction, and 33% of patients in the ribociclib group had at least one dose reduction compared to 3% in the placebo group. Serious adverse events were reported in 29% of ribociclib-treated patients compared to 17% of placebo-treated patients. Of these events, 11% in ribociclib group and 3% in the placebo group were attributed to the study medication. Withdrawal due to adverse events occurred more frequently in the ribociclib group at 17% versus in 6% of patients in the placebo group. These were primarily due to increases in alanine transaminase (ALT) or aspartate aminotransferase (AST).[5]

There were 13 deaths (2.7%) in the ribociclib group and eight deaths (3.3%) in the placebo group during treatment or within 30 days of discontinuing treatment. Most of the deaths (seven in each group) were due to disease progression; however, there was one death in the ribociclib group that was suspected to be related to the study treatment. This patient died from acute respiratory distress syndrome and had baseline lung metastases.

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

1.2.2 Additional Evidence

See Sections 3, 4, and 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (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 fulvestrant for treatment of post-menopausal women with HR-positive, HER2-negative ABC, as initial therapy or following disease progression on ET. Both CBCN and Rethink Breast Cancer provided input based on data collected from two online surveys. Among the most commonly reported symptoms of ABC, fatigue followed by pain were the symptoms rated by respondents to have the most severe impact on QOL; furthermore, the ability to work followed by the ability to sleep were reported to be the most impacted by cancer symptoms. It was reported that 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. Key concerns of 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 treatment option. QOL was also noted to be very important; patients regularly acknowledge the importance of having energy to spend time with family and friends. CBCN and Rethink Breast Cancer were unable to connect with Canadian patients who had experience with ribociclib and fulvestrant. However, Rethink Breast Cancer provided input from nine post-menopausal survey respondents who had HR-

positive, HER2-negative breast cancer and treatment experience with ribociclib but not in combination with fulvestrant. All nine of these women required dose reductions with ribociclib; of whom, seven were receiving ribociclib as initial ET. Overall, these patients felt that ribociclib had improved their cancer symptoms, maintained quality of life, and controlled disease progression. Fatigue and back pain were the most commonly reported side effects of ribociclib; however, respondents mostly found these side effects to be very tolerable.

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 fulvestrant for the treatment of post-menopausal women with HR-positive, HER2-negative ABC as initial therapy or following disease progression on ET. In the second-line setting, it was noted in the joint clinician input that there is presently no funding for CDK 4/6 inhibitors. The combination of fulvestrant and a CDK 4/6 inhibitor was highlighted to be superior to fulvestrant monotherapy and to exhibit an acceptable safety and tolerability profile. The CCO clinicians stated a preference to administer ribociclib over abemaciclib and palbociclib in the endocrine-naive setting. The clinicians noted that abemaciclib has more toxicities and although palbociclib has the most acceptable toxicity profile, the evidence supports the use of ribociclib. The clinicians felt that there is limited evidence to extend the use of ribociclib and fulvestrant to HER2-positive patients; however, they noted that male breast cancer patients should have access to CDK 4/6 inhibitors despite the very limited evidence for use of fulvestrant in men. In the MONALEESA-3 trial males were not excluded but none were recruited. The clinicians stated that AIs plus CDK4/6 inhibitors should be allowed in the second-line setting. Upon progression with ribociclib plus fulvestrant, presumably in the second-line setting, options would include everolimus plus exemestane or chemotherapy. Treatment choice would depend on everolimus availability, prior treatment with ET, and clinical features that may suggest the preferability of chemotherapy. Drug contraindications were reported according to the ribociclib and fulvestrant product monographs; thus, 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. Additionally, fulvestrant was reported to be contraindicated in those with hypersensitivities to the drug or its excipients and in pregnant or lactating women.

Summary of Supplemental Questions

A supplemental issue relevant to the pCODR review and to the PAG were identified while developing the review protocol and can be found in Section 7:

- Summary and Critical Appraisal of a Sponsor-submitted Indirect treatment comparison (ITC)

As the MONALEESA-3 trial did not include a comparison to an active relevant comparator, the sponsor conducted an ITC to estimate the relative efficacy (PFS) and safety of ribociclib plus fulvestrant versus other treatments for patients with HR-positive, HER2-negative ABC. The ITC was conducted in order to provide inputs into the pharmacoeconomic model supporting the reimbursement request. Eligible trials were identified from a systematic review of electronic databases performed in April 2018 seeking RCTs and was supplemented with trials identified through a more targeted review of the literature. The ITC of PFS was conducted using the Bucher method, while adverse events were evaluated using an unanchored (naïve) comparison. The sponsor conducted several ITCs, each with a different patient population derived from the MONALEESA-3 trial: the full trial population, ET sensitive patients receiving first-line therapy (which excluded patients with a disease-free interval <12 months after (neo)adjuvant therapy), ET resistant patients who were either first-line ET refractory or were receiving second-line therapy, or patients receiving second-line therapy only.

A total of 16 trials were included in the ITC, which evaluated treatments including CDK 4/6 inhibitor-based therapies (palbociclib or abemaciclib), AI, fulvestrant, tamoxifen, and everolimus with or without exemestane. Treatment comparisons were dependent on what trials could be connected in each ITC evidence network. Not all trials focused on a post-menopausal population, however the authors tried to obtain subgroup data for post-menopausal patients when available. For the full population, the ITC results showed that all three CDK 4/6 inhibitors when combined with fulvestrant achieved a statistically significant improvement in PFS versus fulvestrant alone. Ribociclib plus fulvestrant was also shown to be superior to exemestane monotherapy, and there was no clear difference in efficacy between ribociclib plus fulvestrant and palbociclib plus fulvestrant or abemaciclib plus fulvestrant. There were no trials of palbociclib or abemaciclib plus fulvestrant in the first-line (ET sensitive), thus comparisons for this patient subgroup were between ribociclib plus fulvestrant and CDK 4/6 inhibitors combined with an AI; results from these comparisons showed no evidence of a difference in efficacy between ribociclib plus fulvestrant and the other CDK 4/6 inhibitors plus an AI. The ITC results for the second-line (ET resistant) and ET refractory subgroups were similar, as these subgroups used the same evidence network; results showed no differences in efficacy between ribociclib plus fulvestrant and the other CDK 4/6 inhibitors plus fulvestrant or everolimus plus exemestane. No conclusions could be drawn about the relative harms of the CDK 4/6 inhibitors, as only a naïve comparison was presented; however, various cytopenias, most notably neutropenia, appear to be an adverse effect associated with the CDK 4/6 inhibitors.

The pCODR Methods Team considered the significant heterogeneity in patient populations among the included trials as a major limitation of the ITC; there were notable differences across the trials related to menopausal status, endocrine partner, disease-free interval, inclusion of de novo ABC patients, and line of therapy, as well as missing information on other important patient and trial characteristics. Overall, the ITC results should be interpreted with caution given the significant clinical heterogeneity across trials that could impact their comparability to the MONALEESA-3 trial and produce biased estimates of relative treatment effect.

See section 7.1 for more information.

Comparison with Other Literature

No relevant 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-3 trial; an assessment of limitations and potential sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence from the MONALEESA-3 trial

Domain	Factor	Evidence: MONALEESA-3[2]	Generalizability Question	CGP Assessment of Generalizability
Population	Age	The median age of patients was 63 years (range, 31-89 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, including those over the age of 75; therefore, the trial results would apply to all post-menopausal females.[7]
	Gender	Males were permitted in the trial, but no males were enrolled.	Do the trial results apply to male patients?	The CGP agree that generalizing the evidence to the male population with ABC may be reasonable given the rarity of the disease in men and considering men were included as part of the inclusion criteria of the trial although none were enrolled.
	Performance status	% of patients in the trial with: ECOG of 0: 64% ECOG of 1: 36% Patients with an ECOG of 2 were excluded.	Are the trial results applicable to patients with an ECOG performance status of 2 or greater?	All phase 2 and 3 randomized trials of CDK 4/6 inhibition have excluded patients with an ECOG PS of 2 or greater hence generalizability to these patients cannot be assumed.
	Disease-free interval	% of patients in the trial with: Newly diagnosed, de novo disease: 19% Non-de novo disease: 81% Disease-free interval of ≤12 months: 4% Disease-free interval of >12 months: 77%	Is the proportion of de novo disease reflective of the Canadian patient population AND are trial results applicable to this patient population?	The distribution of patients with de novo and non-de novo disease observed in the MONALEESA-3 trial is reasonably generalizable to the Canadian population and reflects the particular subgroup of patients that was pre-specified in the trial (Group A).

Domain	Factor	Evidence: MONALEESA-3[2]	Generalizability Question	CGP Assessment of Generalizability
	CNS metastases	Patients with active CNS metastases were excluded from the trial.	Are the trial results applicable to patients with uncontrolled CNS metastases?	Very limited data exists on the role of CDK 4/6 inhibitors for ABC patients with symptomatic and/or untreated 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. It would be reasonable to consider ribociclib plus fulvestrant for patients meeting CNS criteria for the MONALEESA-3 trial inclusion, which included: a) at least 4 weeks from definitive CNS treatment (surgery or radiation); and b) clinically stable, and off steroids and not receiving contraindicated anti-epileptic medication. CNS-specific benefit is unknown and should not be assumed. The trial results are not generalizable to patients with uncontrolled CNS metastases.
	Inflammatory BC	Patients with inflammatory breast cancer were excluded from the trial.	Are the trial results applicable 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	Dosing schedule	Ribociclib was administered 600 mg PO OD, days 1-21 of a 28-day cycle) + Fulvestrant 500mg IM on day 1 of each cycle and day 15 of cycle 1	Is the dosing schedule of fulvestrant applicable to the Canadian practice?	The use of fulvestrant, at the dose and schedule used in the MONALEESA-3 trial is appropriate for the included patient population; however, generalizability to the Canadian population is limited by restricted access to fulvestrant due to funding mechanisms.
	Prior therapy	% of patients in the trial	Prior exposure to	All phase 3 randomized trials

Domain	Factor	Evidence: MONALEESA-3[2]	Generalizability Question	CGP Assessment of Generalizability
		with: No prior (neo)adjuvant ET: 29% Progression on or within 12 months of end of ET: 29% Progression >12 months after end of ET: 21% Patients with previous CDK use and chemotherapy were excluded from the trial.	CDK 4/6 inhibitor-based therapy in the advanced/metastatic setting?	of ABC have excluded patients with prior CDK 4/6 exposure. There is no evidence supporting clinical benefit for patients with prior CDK 4/6 plus AI exposure in the ABC setting. It is unknown if changing the endocrine therapy backbone and continuing with CDK 4/6 therapy (i.e. changing an AI to fulvestrant) provides clinical benefit in the second-line or beyond treatment setting. For patients with disease progression on fulvestrant alone in the advanced setting and without prior exposure to a CDK 4/6 inhibitor, the addition of ribociclib to single-agent fulvestrant could be considered in the setting of small volume, non-life threatening progression, based on the totality of evidence supporting the clinical benefit of CDK 4/6 inhibition as a component of second-line therapy. Although prior exposure to chemotherapy in the advanced setting was not permitted in the trial, it would be reasonable to consider ribociclib plus fulvestrant as a treatment option following completion of first-line chemotherapy.

Domain	Factor	Evidence: MONALEESA-3[2]	Generalizability Question	CGP Assessment of Generalizability
Comparator	Matched Placebo	The comparator in the trial was matched placebo + Fulvestrant 500mg IM on day 1 of each cycle and day 15 of cycle 1 The CGP identified these additional treatments as relevant comparators: • Palbociclib + fulvestrant • Abemaciclib + fulvestrant • Palbociclib + AI • Abemaciclib + AI The sponsor provided an ITC that included indirect comparisons of ribociclib plus fulvestrant to these relevant comparators. Please refer to section 7 for more information.	Are the results of the ITC generalizable to patients who may receive these relevant comparators?	Refer to section 1.1.2 for the CGP's interpretation of the ITC results.

Abbreviations: ABC=advanced or metastatic breast cancer; AI=aromatase inhibitor; BC=breast cancer; 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; OD=once daily; PO=per oral route.

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 due to metastatic disease expected.[8] In Canadian women, breast cancer accounts for approximately 25% of all cancer incidence and 13% of all cancer deaths with 1 in 33 dying of metastatic disease over the course of her lifetime.[8]

Roughly 70-80% of breast cancers are potentially endocrine sensitive and HER2-negative as determined by an analysis of estrogen +/- progesterone receptors (HR-positive) and HER2 expression in the primary tumour and/or in biopsies from a metastatic site of disease. Although treatable, metastatic HR-positive, HER2-negative ABC is an incurable disease with median OS estimated at around three years. Although certain patient subsets can survive for long periods of time on single-agent ET, it is not possible to a priori identify these patients. Similarly, other patients can experience rapidly progressive disease with much shorter OS times.

Most women developing HR-positive, HER2-negative ABC are candidates for single-agent ET with non-curative intent. Classically, this treatment option was most often recommended for those 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. For the post-menopausal patient population, single-agent ET commonly involved tamoxifen or a NSAI (letrozole or anastrozole).

Need

Second-line endocrine-based therapeutic options have historically been limited to a steroidal AI (i.e., exemestane) as a single agent with a median PFS of 3.7 months (range, 3.7-4.5).[9] The combination of exemestane and everolimus was investigated in the BOLERO-2 randomized trial comparing exemestane alone to exemestane plus everolimus.[10] Despite a statistically significant PFS benefit of 4.1 months (HR of 0.43; 95% CI:0.35, 0.5, p<0.001), the analysis of OS did not reveal a statistically significant difference with the addition of everolimus.[11] The most common grade 3 or 4 adverse events attributable to everolimus were stomatitis (8% in the everolimus-plus-exemestane group vs. 1% in the placebo-plus-exemestane group), anemia (6% vs. <1%), dyspnea (4% vs. 1%), hyperglycemia (4% vs. <1%), fatigue (4% vs. 1%), and pneumonitis (3% vs. 0%). Recent evidence suggests that co-administration of a dexamethasone mouthwash can mitigate the stomatitis of everolimus but despite this,[12] uptake of everolimus and exemestane as a standard second-line treatment option for post-menopausal patients with HR-positive, HER2-negative ABC has been limited.

Fulvestrant as single agent has also been evaluated in a number of relevant clinical trials the most recent of which, FALCON, which compared fulvestrant to anastrozole for post-menopausal women with HR-positive, HER2-negative incurable breast cancer who were previously unexposed to ET in the adjuvant or metastatic setting.[13] Fulvestrant was associated with a statistically significant improvement in PFS compared with anastrozole (HR of 0.797; 95% CI: 0.637, 0.999; p=0.0486). Median PFS was 16.6 months (95% CI: 13.83, 20.99) with fulvestrant and 13.8 months (95% CI: 11.99, 16.59) with anastrozole. In patients with measurable disease, the ORR was 46% with fulvestrant and 45% with anastrozole (odds ratio of 1.07; 95% CI: 0.72, 1.61). Median DOR was longer in the fulvestrant group (20.0 months [95% CI: 15.90, 27.63]) than in the anastrozole group (13.2 months [95% CI: 10.64, 16.72]). Adverse events of special interest (joint disorders and

back pain) were reported by 26% of patients in the fulvestrant group and 18% of patients in the anastrozole group. No adverse events of special interest led to treatment interruption or had a fatal outcome. No serious adverse events of special interest were reported.

Despite the above, Canadian patients have limited access to fulvestrant due to funding constraints and the fact that the patient population in the FALCON trial is not broadly represented in the Canadian population as the vast majority of patients with incurable HR-positive, HER2-negative ABC have had prior exposure to ET in the adjuvant setting.

Table 1.3: CDK4/6 inhibitors in ABC: Post-AI trials

Trial	Regimen	Phase	N	ORR*, %	PFS, Months	HR	95% CI
PALOMA-3[14]	Fulvestrant ± palbociclib	3	521	6 vs. 10	4.6 vs. 9.5	0.46	0.36-0.59
MONARCH-2[15,16]	Fulvestrant ± abemaciclib	3	669	21 vs. 48	9.3 vs. 16.4	0.55	0.45-0.68
MONALEESA-3[2,4]	Fulvestrant ± ribociclib	3	345	29 vs. 41	12.8 vs. 20.5	0.59	0.48-0.73

*Patients with measurable disease

MONALEESA-3 is one of three large RCTs that have investigated the addition of a CDK 4/6 inhibitor to fulvestrant in post-menopausal patients with incurable HR-positive, HER2-negative ABC (Table 1.3). All the trials evaluated investigator-assessed PFS as the primary endpoint but they varied in terms of inclusion criteria. PALOMA-3 was the only trial to allow prior chemotherapy for advanced disease (33% of the trial population) with 38.1% of the patient population also having had two or more prior lines of therapy for ABC. In contrast, MONALEESA-3 and MONARCH 2, which investigated the CDK4/6 inhibitor abemaciclib versus placebo plus fulvestrant, did not include patients with two or more prior lines of therapy and excluded patients receiving first-line chemotherapy in the metastatic setting. Both MONARCH-2 and MONALEESA-3 demonstrated a statistically significant OS benefit that favoured the addition of a CDK4/6 inhibitor to fulvestrant (MONARCH-2: absolute OS advantage of 9.4 months; HR of 0.76, 95% CI: 0.61-0.95; p=0.01; MONALEESA-3: median OS not reached versus 40 months; HR of 0.72;,95% CI: 0.57-0.92; p=0.00455), whereas PALOMA-3 observed an absolute OS benefit of 6.9 months (HR of 0.81, 95% CI: 0.64-1.03; p=0.09), which was not statistically significant. Differences in trial inclusion criteria likely account for the divergent OS results between these trials.

Patient input for this submission was supplied by the CBCN and Rethink Breast Cancer, and included information obtained from two online patient surveys of patients with HR-positive breast cancer, who cited key concerns related to management of their disease that 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 treatment alternative. The CBCN and Rethink Breast Cancer patient groups were unable to connect with Canadian patients who had experience with ribociclib and fulvestrant.

Effectiveness

MONALEESA-3 is a phase 3, randomized, double-blind, placebo-controlled trial for post-menopausal women with incurable HR-positive, HER2-negative ABC that randomized patients to either ribociclib plus fulvestrant or placebo plus fulvestrant.[2,4] A number of eligibility criteria related to prior treatment exposure in the advanced setting allowed for the inclusion of patients in either the first-line (total n=367; 49.2% of the ribociclib group) or second-line setting (total n=345; 48.8% of the ribociclib group) after disease

progression on first-line ET. Patients with prior chemotherapy for ABC were not permitted in the trial.

The primary outcome, investigator-assessed PFS, was significantly improved in the ribociclib plus fulvestrant group (all patients), with a median PFS of 20.5 months (95% CI: 18.5, 23.5 months) versus 12.8 months (95% CI: 10.9-16.3 months), respectively, and a HR of 0.59 (95% CI: 0.48, 0.73; p< 0.001). The PFS HR was 0.58 (95% CI: 0.42, 0.80) in patients who were treatment naïve in the advanced setting and was 0.57 (95% CI: 0.43, 0.74) in patients who had received up to one line of ET for advanced disease. The ORR was 32.4% (95% CI: 28.3, 36.6) versus 21.5% (95% CI: 16.3, 26.7) favouring ribociclib plus fulvestrant in all patients, and 40.9% (95% CI: 35.9, 45.8) versus 28.7% (95% CI: 22.1, 5.3) among patients with measurable disease at baseline.

The second pre-specified interim analysis of OS was performed with a median follow-up for all patients of 39.4 months. At the data cut-off date for this analysis, the Kaplan-Meier estimated OS was estimated to be 57.8% (95% CI: 52.0, 63.2) in the ribociclib group and 45.9% (95% CI: 36.9, 54.5) in the placebo group. A statistically significant OS benefit was observed in the ribociclib group as compared to the placebo group, with a 28% difference in the relative risk of death (HR of 0.72; 95% CI: 0.57, 0.92) that crossed the prespecified O'Brien-Fleming stopping boundary (p=0.00455). These data represent the final analysis of OS.

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 treatment groups, with 81.5% of patients in the ribociclib plus fulvestrant group and 84.7% of patients in the placebo plus fulvestrant group receiving post-progression therapies. Chemotherapy was received as first post-progression treatment by 35.9% of patients in both groups. These data suggest that significant differences in post-progression treatments between the treatment groups are unlikely to have impacted the observed OS benefit.

Patient-reported HRQOL was evaluated as an exploratory outcome of MONALEESA-3, with the primary patient-reported outcome of interest being time-to-10% deterioration in the global health status/QOL subscales of the EORTC-QLQ- CLC30. A definitive 10% deterioration was defined as a worsening of score by 10% or more when compared to baseline, with no later improvement above this threshold during the treatment period, or death due to any cause. Baseline assessments for the EORTC-QLQ-C30 were obtained from 93% of patients in MONALEESA-3, however, by the time end of treatment assessments were performed, data was were only available from 41% of patients.[6] The CGP noted the pCODR Methods Team's assessment that the amount of missing data introduces the potential for bias in the assessment of HRQOL since remaining patients are likely inherently different compared to patients 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 median time-to-definitive 10% deterioration in global health status/QOL was not reached for the ribociclib plus fulvestrant group and was 19.4 months in the placebo plus fulvestrant group (HR of 0.80 [95% CI: 0.60, 1.05]). The HRs for time-to-deterioration for the other scales assessed (QLQ-C30 emotional, social and physical functioning; all BPI-SF pain scales; and the EQ-5D-5L VAS) numerically favoured ribociclib plus fulvestrant but the CIs indicated no difference between the treatment groups.

Safety

The most common grade 3 and 4 adverse events occurring in ≥ 10% of patients in the ribociclib plus fulvestrant treatment group were neutropenia and leukopenia with the only grade 4 event reported in ≥ 5% of patients being neutropenia. Febrile neutropenia occurred

in 1% of patients in the ribociclib plus fulvestrant group compared to 0% of patients in the placebo plus fulvestrant group.

QTcF prolongation (any grade) occurred in 6.2% of patients receiving ribociclib plus fulvestrant compared to 0.8% of patients receiving placebo plus fulvestrant. Three patients (0.6%) in the ribociclib plus fulvestrant group and no patients in the placebo plus fulvestrant group discontinued study treatment because of a prolonged QTcF interval; and there were no cases of torsades de pointes in the trial.

Serious adverse events occurred in 28.6% and 16.6% in the ribociclib plus fulvestrant and placebo plus fulvestrant groups, respectively; of these, 11.2% and 2.5%, respectively, were attributed to the study medication. The most common all-grade all-causality serious adverse events reported in ≥ 1% of patients (ribociclib plus fulvestrant versus placebo plus fulvestrant) were pneumonia (1.9% vs. 0%) and dyspnea (1.2% vs. 2.1%). In the ribociclib plus fulvestrant group, grade 3 or 4 elevated ALT occurred in 6.6% and 1.9% of patients, respectively; and elevated AST occurred in 4.8% and 1.2% of patients, respectively. In the placebo plus fulvestrant group, grade 3 ALT and AST events occurred in one (0.4%) and two patients (0.8%), respectively, and there were no grade 4 elevated ALT or AST events. Two patients receiving ribociclib plus fulvestrant were confirmed cases of Hy's law and their liver enzymes returned to normal after discontinuation of ribociclib.

Ribociclib requires more extensive safety assessments (electrocardiograms [ECG], Liver function tests) compared to the 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.

Other Considerations

The PAG raised several points to be considered if ribociclib combined with fulvestrant 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:

- The appropriateness of adding ribociclib for patients who are already on fulvestrant but who have not yet progressed: although not specifically investigated in the MONALEESA-3 trial, the possible addition of ribociclib for a post-menopausal woman currently on fulvestrant whose disease has not progressed could be considered.
- Switching patients who are already on other ET but who have not yet progressed, to ribociclib plus fulvestrant: a switch in ET could be considered, however, it would also be reasonable to continue with first-line therapy reserving ribociclib plus fulvestrant for second-line treatment upon disease progression.
- Switching to a different CDK 4/6 inhibitor (ribociclib with abemaciclib or palbociclib) for the respective indication 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 fulvestrant would be reasonable.
- In regard to PAG's questions about the appropriate sequencing of all available treatments, specifically:

- Whether there is a 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.
- Whether there is a preference for CDK 4/6 inhibitor (e.g., ribociclib, abemaciclib, or palbociclib) and if they can be considered therapeutically equivalent: the sponsor performed an ITC to estimate the relative treatment effects of CDK 4/6 inhibitor combinations in different groups of patients from the MONALEESA-3 trial (full trial population, treatment naïve patients [first-line], and endocrine resistant patients [second-line]) but a critical appraisal of this analysis performed by the pCODR Method's Team indicated the results should be interpreted with caution due to the heterogeneity in patient populations across the included trials that could impact their comparability to the MONALEESA-3 trial and lead to biased estimates of relative treatment effect (refer to Section 7). 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.
- Treatments patients can receive following disease progression on ribociclib plus fulvestrant: treatment options after disease progression on ribociclib plus fulvestrant can include single-agent AI (non-steroidal or steroidal AI), tamoxifen, everolimus plus exemestane, or single-agent/combination cytotoxic chemotherapy, as well as clinical trial options depending on availability. In MONALEESA-3, post-progression receipt of a CDK 4/6 inhibitor was 11% in the ribociclib group and 25.4% 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 retreatment with ribociclib or another CDK 4/6 inhibitor in patients whose disease has progressed on or after ribociclib plus fulvestrant: there is no evidence supporting retreatment with a CDK 4/6 inhibitor in the setting of disease progression on a CDK 4/6 inhibitor.
- Sequencing of everolimus plus exemestane: everolimus plus exemestane remains a treatment option for this patient population after disease progression on a CDK 4/6 inhibitor; however, it is unclear as to whether the clinical benefit of this combination is maintained in the context of prior CDK 4/6 exposure. Due to the robust nature of the clinical data supporting CDK 4/6 inhibitors as first-line therapy, as well as the fact that the majority of patients in the BOLERO-2 RCT supporting everolimus and exemestane were treated in the second-line setting, 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 fulvestrant for post-menopausal women with incurable HR-positive, HER2-negative ABC in the first- or second-line setting based on the strength of one high-quality randomized, double-blind, placebo-controlled trial demonstrating a clinically meaningful

and statistically significant PFS and OS benefit along with an acceptable safety profile and no apparent detriment on HRQOL.

- The safety analysis of ribociclib plus fulvestrant in the MONALEESA-3 trial did not reveal unexpected toxicities in this patient population.

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.[17] 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, endocrine therapy, radiation and targeted therapy). It is also estimated that, in Canada, approximately 5-10% of women present with de novo ABC. ABC remains incurable and is treated systemically with palliative intent with a median life expectancy of approximately 2-3 years.[18]

The goals of palliative systemic therapy are threefold: to maintain or improve QOL, 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 (HR and HER2 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.[19] In the absence of rapidly progressive disease or visceral crisis, endocrine-based therapy is usually considered first-line palliative treatment in HR-positive, HER2-negative disease, based on its efficacy and favourable toxicity profile. Commonly used options include selective estrogen receptor modulators (e.g. tamoxifen), AI (e.g. anastrozole, letrozole, and exemestane), selective estrogen receptor degraders (e.g. fulvestrant), and less commonly, progesterone agents (e.g. megestrol acetate). AI and fulvestrant are only appropriate for post-menopausal patients whereas tamoxifen is effective regardless of menopausal state. Ovarian suppression with LHRH analogues may also be employed in conjunction with systemic endocrine therapy. 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 ET 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.

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, location and involvement of tumour 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.[20] 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.[10] 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 CDKs. CDKs 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 has 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. CDK4/6 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.[21-26]

Ribociclib is an orally administered, selective small molecule inhibitor of CDK 4/6 administered on a three-week daily schedule followed by a 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 is both ECG and serum chemistry monitoring recommendations.

Earlier trials have demonstrated both tolerability and clinical benefit and ribociclib has now been investigated in three large RCTs:

- MONALEESA-2: ribociclib plus letrozole versus placebo plus letrozole
- MONALEESA-3: ribociclib plus fulvestrant versus placebo plus fulvestrant
- MONALEESA-7: ribociclib + 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 fulvestrant for the treatment of HR-positive, HER2-negative ABC would be the same population included in the MONALEESA-3 trial. This includes post-menopausal women with incurable HR-positive, HER2-negative locally advanced or metastatic breast cancer at any time point after curative-intent treatment, those presenting with de novo incurable disease, or those who have received up to one prior line of ET for their

advanced disease. Patients had to have adequate performance status (ECOG performance status of 0-1) as well as adequate organ and bone marrow function.

MONALEESA-3 excluded patients who received prior chemotherapy as well as those having received greater than one line of ET in the advanced setting. Whether the clinical benefit of ribociclib plus fulvestrant 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 trials.

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.

Male patients were eligible for the MONALEESA 3 trial although none were accrued in the trial. Similarly, to all other therapies for male breast cancer where recommendations for treatment are extrapolated from the female patient population, male patients could be considered for ribociclib-based therapy as long as all other general criteria are met.

In Canada, funding access to fulvestrant remains highly restricted which limits the patient population potentially eligible for the combination of ribociclib and fulvestrant.

Although the clinical trial data always started fulvestrant and ribociclib concurrently, there may be situations within the Canadian context where patients have access to and are treated with single agent fulvestrant. In these situations, it would be reasonable to consider the addition of ribociclib to ongoing fulvestrant as long as all other criteria are met for ribociclib consideration. At the time of disease progression on fulvestrant, the addition of ribociclib could be considered in the setting of small volume, non-life-threatening progression, based on the totality of evidence supporting the clinical benefit of CDK 4/6 inhibition as a component of second-line therapy.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The CBCN and Rethink Breast Cancer provided input on ribociclib (KISQALI) in combination with fulvestrant for treatment of post-menopausal women with HR-positive, HER2-negative ABC, as initial therapy or following disease progression on endocrine-based therapy. 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 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 ABC 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; of those, 42 were also HER2-negative (HR-positive, HER2-negative breast cancer). 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" had 71 patient and 16 caregiver respondents; patients were contacted through membership databases of the CBCN and other patient organizations. This survey was conducted in collaboration with Rethink Breast Cancer. Of note, none of the patient respondents had experience with ribociclib plus fulvestrant.

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 from 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. Among the 26 women respondents, 13 were from Canada with representation from Alberta, BC, Ontario, Quebec, and Saskatchewan; six were from Australia; five were from the US; and two were from the UK. Of note, no patient respondents of Rethink Breast Cancer's survey had experience with ribociclib and fulvestrant.

Among the most commonly reported symptoms of advanced and metastatic breast cancer, fatigue followed by pain were the symptoms rated to have the most severe impact on quality of life; furthermore, the ability to work followed by the ability to sleep were reported to be the most impacted by cancer symptoms. It was reported that 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. The CBCN noted that the value of extending the time that one's cancer is progression-free 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. The CBCN and Rethink Breast Cancer patient groups were unable to connect with Canadian patients who had experience with ribociclib and fulvestrant. However, Rethink Breast Cancer provided input from nine post-menopausal survey respondents who were HR-positive, HER2-negative breast cancer patients with treatment experience with ribociclib but not in combination with fulvestrant. All nine of these women required dose reductions with ribociclib; of whom, seven were receiving ribociclib as initial endocrine therapy. Overall, these patients felt that ribociclib had improved their cancer symptoms, maintained quality of life, and controlled disease progression. Fatigue and back pain were the most commonly reported side effects of ribociclib; however, respondents mostly found these side effects to be very tolerable.

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) 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) ▪ 9 patients were postmenopausal, of whom: o 7 patients received ribociclib as initial endocrine therapy

3.1 Condition and Current Therapy Information

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

The CBCN's 2017 survey highlighted the key concerns of the 65 respondents with HR-positive breast cancer (42 of whom had HR-positive, HER2-negative disease) 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 and a small fraction (two patients) had 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; 54% and 37% of patients reported that fatigue and pain resulted in a significant or debilitating impact, respectively. Moreover, the social impact of ABC was evident from CBCN's 2017 survey responses; 12% of respondents were employed full-time at the time of the survey compared to 47% 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%). 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 marital 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 on a scale from 1 (no impact) to 5 (significant impact) the impact of ABC symptoms on their quality of life and how symptoms associated with breast cancer have impacted their day-to-day activities. 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 on 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 Advanced or Metastatic Breast Cancer

Among the 65 HR-positive breast cancer patient respondents of CBCN's 2017 survey, most of the patients (n=56) had been treated with surgery, 48 had undergone radiation therapy, 48 had received hormone therapy, and 51 had been previously treated with chemotherapy. The CBCN's review of current studies and grey literature 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;

moreover, 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, which is needed 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 to treatment.

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

Table 3.2. Treatment experience of HR-positive, HER2-negative advanced or metastatic breast cancer, 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%)
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 patients 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 respond. Of note, the specific treatments that elicited these responses were not specified. Regarding side effects, fatigue was the most commonly reported among these treatments (88%, n=24), followed by low blood cell counts (58%) and insomnia (54%). Additionally, fatigue was most commonly cited by respondents as the most difficult side effect to tolerate; although, insomnia, hair loss, joint pain, nausea, and back pain were also cited by multiple respondents.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for Ribociclib and Fulvestrant

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 PFS was indicated to be of critical concern for metastatic patients according to the CBCN. The CBCN stated that the value of extending the time that a patients' cancer is progression-free 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— even if benefits are as minimal as a six-month extension of progression-free disease. 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.

According to the CBCN's 2017 survey, treatment efficacy was reported to be critical to HR-positive ABC patients; 98% of respondents indicated that progression-free survival (PFS) of six months or more would influence their treatment decisions; and 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 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, concentration problems, 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 a 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 progression-free disease 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; 34% indicated they were willing to accept serious treatment risk if it would control the 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."*

In summary, the CBCN highlighted that treatments that alleviate cancer-related symptoms with minimal side effects allow 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 and Fulvestrant

The CBCN was unable to connect with Canadian patients who had experience with ribociclib plus fulvestrant; however, the CBCN noted the importance of access to multiple treatment options for patients in the advanced and metastatic setting based on data obtained from their surveys and previous submissions for ABC treatments. They also noted that patients continuously indicate the importance of treatments that allow for a good quality of life, which is provided by ribociclib as the data from the clinical trials demonstrate that ribociclib is well tolerated by patients, offers a good quality of life, and improves PFS.

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, nine were post-menopausal; however, none received ribociclib in combination with fulvestrant. Among the post-menopausal women, seven patients received ribociclib as initial endocrine therapy, one patient was treated with ribociclib for zero to three months, four patients were treated for six to twelve months, and four patients were treated for more than one year. Notably, all required dose reductions during their treatment. Upon completion of the survey, six patients were still being treated with ribociclib, one patient completed her course of treatment, one patient could not tolerate the side effects, and one was removed from the clinical trial. The data presented below reports the experience of post-menopausal women with HR-positive and HER2-negative advanced or metastatic breast cancer who were treated with ribociclib but not in combination with fulvestrant.

Patients were asked to rate the change to their quality of life elicited by ribociclib compared to other treatments they had received on a scale of 1 (much worse) to 5 (much better). Respondents felt that ribociclib had improved their cancer symptoms, maintained their quality of life, and controlled disease progression. Namely, patients reported that ribociclib helped address fatigue, loss of appetite, and dyspnea caused by the cancer. Patients were less positive about the drug's side effects and their ability to perform regular activities but ribociclib had a particular negative affect on the ability to sleep (lowest average score of 2.9). All ratings are summarized 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%	14.3%	28.6%	0.0%	57.1%	4.0
Drug side effects	14.3%	28.6%	14.3%	0.0%	42.9%	3.3
Maintaining quality of life	0.0%	0.0%	33.3%	16.7%	50.0%	4.2
Controlling disease progression	0.0%	0.0%	28.6%	14.3%	57.1%	4.3
Ability to work	33.3%	0.0%	33.3%	0.0%	33.3%	3.0
Ability to sleep	14.3%	14.3%	42.9%	28.6%	0.0%	2.9
Ability to drive	0.0%	0.0%	57.1%	14.3%	28.6%	3.7
Ability to perform household chores	14.3%	0.0%	28.6%	28.6%	28.6%	3.6
Ability to care for children	0.0%	0.0%	50.0%	25.0%	25.0%	3.8

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

Fatigue and back pain were the most commonly reported side effects of ribociclib (67% each, n=9) followed by hot flashes (56%), neutropenia, diarrhea, and joint pain (44% each). However, respondents mostly found these side effects to be very tolerable. When asked how much they could tolerate the side effects associated with ribociclib on a scale of 1 (completely tolerable) to 10 (completely intolerable), the average score was 7.86. Notably, the only selected ratings were 4, 5, 8, and 10 with the most frequent rating being 10 (completely intolerable) as depicted in Table 3.5.

Table 3.5 Scoring of the tolerability of side effects associated with ribociclib, modified from Rethink Breast Cancer

Rating	Responses (%)	Rating	Responses (%)
1	0.0%	6	0.0%
2	0.0%	7	0.0%
3	0.0%	8	25.0%
4	12.5%	9	0.0%
5	12.5%	10	37.5%

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

Additionally, patients were asked if side effects became worse over time on a scale of 1 (not at all worse) to 5 (much worse). Half of all respondents answered 1. However, others did experience symptom worsening resulting in an average score of 2.6. The most frequent rating was 1 (not at all worse) as reported in Table 3.6.

Table 3.6. Scoring of the worsening of side effects overtime associated with ribociclib, modified from Rethink Breast Cancer

Rating	Responses (%)
1	50.0%
2	12.5%
3	12.5%
4	0.0%
5	25.0%

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

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 comparator in MONALEESA-3 was fulvestrant and fulvestrant is not publicly funded in any provinces for metastatic breast cancer. PAG is seeking information on data comparing ribociclib plus fulvestrant to currently available treatments.

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 3 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 HER2-positive breast cancer (e.g., HR-positive, HER2-positive metastatic breast cancer who are not eligible for further anti-HER2 treatments).

The MONALEESA 3 trial excluded patients if they had received prior treatment with chemotherapy (except for neoadjuvant/ adjuvant chemotherapy), fulvestrant or any CDK4/6 inhibitor; PAG is seeking confirmation that these subgroups of patients would not be eligible for treatment with ribociclib.

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

- adding ribociclib for patients who are already on an ET (e.g., anastrozole or

letrozole if endocrine-naive or fulvestrant if endocrine-resistant) but not yet progressed
- use with 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 first-line single agent endocrine therapy or second-line and beyond chemotherapy, would need to be addressed on a time-limited basis.

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.

At the time of this PAG input, fulvestrant is not funded in any provinces. PAG noted that this a barrier to implementation. Fulvestrant is available as 250 mg pre-filled syringes. Pharmacy preparation is not required and there is no wastage concern as the dose is 500mg given as two separate injections. This is an enabler to implementation. Fulvestrant would require additional nursing resources and chair time. PAG noted that fulvestrant must be refrigerated and as fulvestrant comes in a large box more fridge space will be required.

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, HER-2 negative breast cancer and the high cost of the combination compared to letrozole or anastrozole alone and other aromatase inhibitors. 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.

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

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate sequencing of all available treatments for HR+, HER2- advanced breast cancer:

- PAG noted that ribociclib plus an AI 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 fulvestrant?
- 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 fulvestrant for the treatment of post-menopausal women with HR-positive, HER2-negative ABC as initial therapy or following disease progression on ET. Various AIs such as anastrozole, exemestane, and letrozole are available in Canada for the initial treatment of HR-positive, HER2-negative breast cancer in the advanced or metastatic setting. Additionally, CDK inhibitor combinations are variably available across Canada; palbociclib plus letrozole is available in almost all jurisdictions, ribociclib plus letrozole as an initial endocrine-based therapy is under provincial consideration, and abemaciclib in combination with an AI or fulvestrant recently received a positive conditional reimbursement recommendation following pCODR review. In the second-line setting, it was noted in the joint clinician input that there is presently no funding for CDK 4/6 inhibitors. The combination of fulvestrant and a CDK 4/6 inhibitor was highlighted to be superior to fulvestrant monotherapy and to exhibit an acceptable safety/tolerability profile. The CCO clinicians would prefer to administer ribociclib over abemaciclib and palbociclib in the endocrine-naive setting. The clinicians noted that abemaciclib has more toxicities and although palbociclib has the most acceptable toxicity profile, the evidence supports the use of ribociclib. The CCO clinicians felt that there is limited evidence to extend the use of ribociclib and fulvestrant to HER2-positive patients; however, they noted that male breast cancer patients should have access to CDK 4/6 inhibitors despite the very limited evidence for use of fulvestrant in men. Namely, in the MONALEESA-3 trial, males were not excluded but none were recruited. Moreover, the clinicians stated that AIs plus CDK4/6 inhibitors should be allowed in the second-line setting. Upon progression with ribociclib plus fulvestrant, presumably in the second-line setting, options would include everolimus plus exemestane or chemotherapy. Treatment choice would depend on everolimus availability, prior treatment with endocrine therapy, and clinical features that may suggest the preferability of chemotherapy. Drug contraindications were reported according to the ribociclib and fulvestrant monographs; thus, 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. Additionally, fulvestrant was reported to be contraindicated in those with hypersensitivities to the drug or its excipients and in pregnant or lactating women. Moreover, 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 Treatments for HR-positive, HER2-negative Advanced or Metastatic Breast Cancer

The CCO clinicians noted that currently, there is no funding for CDK4/6 inhibitors in the second-line setting.

5.2 Eligible Patient Population

Implementation Questions: The eligibility criteria for the MONALEESA-3 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 fulvestrant to (provided all other eligibility criteria are met):

a) HER2-positive breast cancer (e.g., HR-positive, HER2-positive metastatic breast cancer who are not eligible for further anti-HER2 treatments)

The CCO clinicians stated that there is limited evidence in clinical practice on the use of ribociclib plus fulvestrant in the HER2-positive setting; thus, it is reasonable to exclude these patients from this therapy at this time.

b) Male breast cancer

The CCO clinicians noted that male breast cancer patients should have access to CDK 4/6 inhibitors; however, there is very limited evidence for the use of fulvestrant in men. Namely, in the MONALEESA-3 trial, males were not excluded but none were recruited.

c) Use with aromatase inhibitors instead of fulvestrant

The CCO clinicians reported that AIs plus CDK4/6 inhibitors should be allowed in the second-line setting; however, they did not directly comment on their preference between administering AIs or fulvestrant.

5.3 Relevance to Clinical Practice

The CCO clinicians who provided input had experience administering ribociclib plus fulvestrant. They noted that the combination of fulvestrant and a CDK 4/6 inhibitor is superior to fulvestrant monotherapy and has an acceptable safety/tolerability profile. Namely, therapies such as abemaciclib tend to be associated with more toxicities. Moreover, the clinicians highlighted that fulvestrant is not included in the Ontario Drug Benefit so patient access is difficult for those without insurance. Further, the clinicians reported the contraindications as per the monographs.

Contraindications for ribociclib include:

- 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.

Contraindications for fulvestrant include:

- Patients with known hypersensitivity to fulvestrant or to any of its excipients.
- Pregnant or lactating women.

5.4 Sequencing and Priority of Treatments with Ribociclib plus Fulvestrant

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 fulvestrant was available,

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

The CCO clinicians stated a preference of ribociclib over palbociclib and abemaciclib based on the MONALEESA-7 trial. The results of this clinical trial support the use of ribociclib plus an AI

and a LHRH agonist as first-line therapy. Although, the toxicity profile of palbociclib is the most acceptable, the evidence supports the use of ribociclib. As mentioned, abemaciclib tends to be associated with more toxicities. In their input, the CCO clinicians referred to the MONALEESA-7 trial, which is the clinical trial investigating ribociclib as treatment for HR-positive, HER2-negative advanced breast cancer. Of note, the MONALEESA-3 trial is the pivotal trial for this review, which assesses ribociclib plus fulvestrant as treatment for post-menopausal women with HR-positive, HER2-negative advanced breast cancer. The pCODR review team sought clarification if the MONALEESA-3 trial was intended to be included in the clinicians' input for this submission; and if so, pCODR requested a revised response to the above-mentioned question. However, we were unable to receive confirmation by the time this report was being finalized.

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

The CCO clinicians noted their preference for administering ribociclib in combination with an AI and a LHRH agonist, over ribociclib plus fulvestrant, in the endocrine-naïve setting based on the findings of 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 stated that upon progression with ribociclib and fulvestrant, presumably in the second-line setting, options would include everolimus plus exemestane or chemotherapy. The treatment choice would depend on the availability of everolimus, prior endocrine therapy treatment, 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 in combination with fulvestrant as initial treatment or following disease progression on ET in post-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 RCTs	Post-menopausal women with HR-positive, HER2-negative ABC Subgroups: • Initial therapy versus following progression on endocrine therapy	Ribociclib 600mg by mouth once daily for 21 days, followed by 7 days off treatment, combined with fulvestrant, as initial therapy or following disease progression on endocrine therapy.	Endocrine therapy alone: • Estrogen receptor down regulator (e.g. fulvestrant) • AI (e.g., letrozole, anastrozole, exemestane) • Selective estrogen receptor modulator (e.g. tamoxifen) CDK 4/6 inhibitors in combination with endocrine therapy: • CDK 4/6 inhibitor (e.g., ribociclib, palbociclib, abemaciclib) + AI • CDK 4/6 inhibitor (e.g., palbociclib, abemaciclib) + estrogen receptor down regulator (e.g. fulvestrant) • Everolimus + exemestane • Chemotherapy	***Efficacy:*** • **OS** • PFS • ORR • Time-to-response • DOR • **HRQOL** • **Time-to-chemotherapy** ***Harms:*** • AEs • SAEs • WDAEs • Mortality Notable harms: QT prolongation, hepatotoxicity, neutropenia, fatigue

Abbreviations: ABC=advanced or metastatic breast cancer; AE=adverse event; AI=aromatase inhibitor; CDK=cyclin dependent kinase; DOR=duration of response; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; HRQOL=health-related quality of life; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RCT=randomized controlled trial; SAE=serious adverse event; WDAE=withdrawal due to adverse event.

Notes:

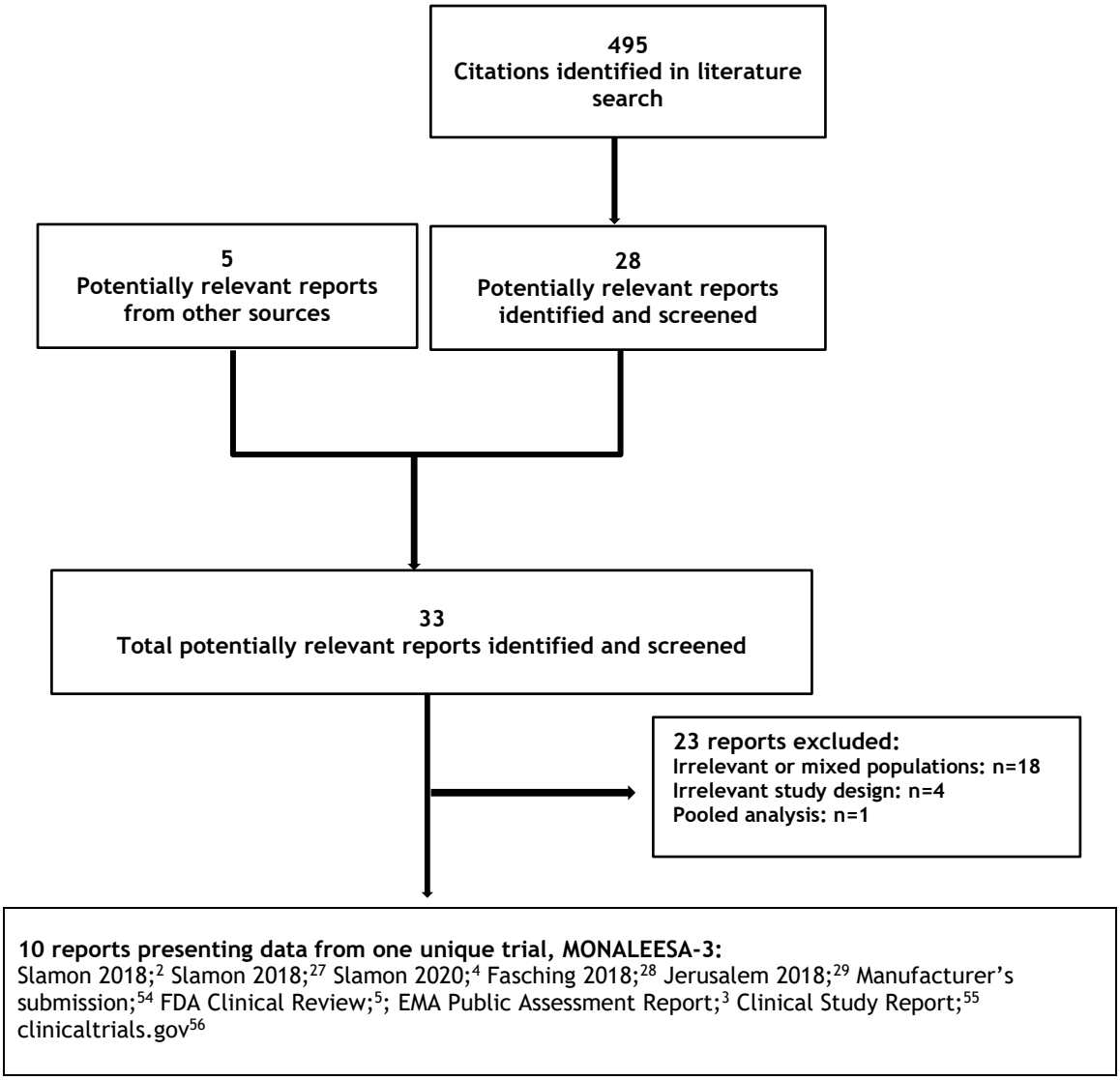
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)

6.3 Results

6.3.1 Literature Search Results

Of the 33 potentially relevant reports identified, 10 reports presenting data from one trial were included in the pCODR systematic review[4,27-31] and 23 reports were excluded. Studies were excluded because they included irrelevant or mixed patient populations,[25,32-48] were a pooled analysis of data from MONALEESA-2, -3, and -7,[49] or had a irrelevant study design.[50-53]

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



Note: Additional data related to MONALEESA-3 were also obtained through requests to the sponsor by pCODR[6]

6.3.2 Summary of Included Studies

One international RCT, MONALEESA-3, which compared ribociclib plus fulvestrant to placebo plus fulvestrant in post-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-3 trial

Trial Design	Key Eligibility Criteria	Intervention and Comparator	Trial Outcomes

MONALEESA-3
 	
Phase 3, double-blind RCT, placebo controlled
 	
Randomization 2:1
 	
N= 726 randomized and treated
 	
174 sites in 30 countries (Asia, Australia, Europe, South America, and North America (including Canada)
 	
Patient Enrolment Dates: June-2015 to June 2016
 	
Data cut-off date: November 3, 2017
 	
Final Analysis Date: February 2020
 	
Funding: Novartis Pharmaceuticals
	Inclusion criteria:
	• Male or female ≥ 18 years old
	• Post-menopausal defined either by:
	  ○ Prior surgical bilateral oophorectomy (with or without hysterectomy)
	  ○ Age ≥ 60
	  ○ Age < 60 and amenorrheic for ≥12 months in absence of CT, TAM, TOR, or ovarian suppression, and FSH and EE2 in the POMP range per local normal range
	• Histologically and/or cytologically confirmed HER2-negative ER+ and/or PR+ BC
	• Patients with either measurable disease (i.e. ≥1 measurable lesion per RECIST 1.1) or ≥1 predominantly lytic bone lesion
	• Patients with ABC (loco regionally recurrent not amenable to curative therapy (e.g. surgery and/or RT) or MBC. Patients could be:
	  ○ Newly diagnosed ABC/MBC, treatment naïve.
	  ○ Relapse >12 months from completion of (neo) adjuvant ET with no treatment for advanced/metastatic disease
	  ○ Relapse ≤12 months from completion of (neo) adjuvant ET with no treatment for advanced/metastatic disease
	  ○ Relapse >12 months from completion of (neo) adjuvant ET then subsequently progressed with documented evidence of progression after one line of ET (with either an anti-estrogen or an AI) for advanced/metastatic disease.
	  ○ ABC/MBC at diagnosis that progressed with one line of endocrine therapy (with either an anti-estrogen or an AI)
	• ECOG PS 0 or 1
		Ribociclib 600 mg PO OD, days 1-21 of a 28-day cycle) +
		FUL 500mg IM on day 1 of each cycle and day 15 of cycle 1
		
		VERSUS
		
		Matching placebo +
		FUL 500mg IM on day 1 of each cycle and day 15 of cycle 1
		
		Treatment continued until disease progression, unacceptable toxicity, death or discontinuation for any other reason
			<u>Primary</u>: PFS
			
			<u>Key Secondary</u>: OS
			
			<u>Other secondary:</u>
			• ORR and CBR
			• TTR
			• DOR
			• Time-to-deterioration in ECOG PS
			• HRQOL

Trial Design	Key Eligibility Criteria	Intervention and Comparator	Trial Outcomes
	• Adequate organ and bone marrow function Exclusion criteria: • Patients who relapsed with documented evidence of relapse ≤12 months from completion of (neo) adjuvant ET and then subsequently progressed with documented evidence of progression after one line of ET (with either an anti-estrogen or an AI) for ABC/MBC • Received prior treatment with CT, fulvestrant, or any CDK4/6 inhibitor • Inflammatory BC • Symptomatic visceral disease • Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality including a QT interval corrected for heart rate according to Frederica's formula (QTcF) > 450 ms • Patients with CNS involvement unless met ALL of the following: o At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment. o Clinically stable CNS tumour at the time of screening and not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases		

Abbreviations: ABC=advanced breast cancer; AI=aromatase inhibitor; BC=breast cancer; CBR=clinical benefit rate; CDK=cyclin dependent kinase; CNS=central nervous system; CT=chemotherapy; DBRCT=double blind randomized controlled trial; DOR=duration of response; ECOG=Eastern Cooperative Oncology Group; EE2=ethinyl estradiol; ER+ = estrogen receptor positive; ET=endocrine therapy; FSH=follicle stimulating hormone; FUL=fulvestrant; HRQOL=health related quality of life; MBC=metastatic breast cancer; OD= once daily; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PO=by mouth; POMP=postmenopausal; PR+ = progesterone receptor positive; PS=performance status; RECIST=response evaluation criteria in solid tumours; RT=radiation therapy; TAM=tamoxifen; TOR=toremifine; TTR=time-to-response.

Sources: Slamon 2018;[2] Slamon 2020;[4] FDA Clinical Review;[5] clinicaltrials.gov[56]

Table 6.3: Select quality characteristics of the MONALEESA-3 trial

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
MONALEESA-3 Sponsor-funded[b]	Ribociclib + FUL versus Placebo + FUL	PFS	364 PFS events to provide 95% power to detect a HR of 0.67, corresponding to an increase in median PFS of 13.4 months[a]	N=726	IRT	All trial personnel remained blinded until database lock	DB Matched placebo	Yes	Yes-for the primary outcome	No	Yes

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

Notes:

[a] The required sample size was based on the following assumptions: The median TTP for fulvestrant in first-line post-menopausal advanced breast cancer patients was estimated to be between eight months (Howell 2004) and 23 months in the FIRST trial (Robertson et al 2012). For sample size calculation, the median PFS for first-line patients was assumed to be 18 months. The median PFS for fulvestrant in relapsed advanced breast cancer was estimated to be between 4.8 months (SoFEA trial) and 6.5 months (CONFIRM trial). Since the MONALEESA-3 patient population is closer to the population in CONFIRM, for sample size calculation, the median PFS for fulvestrant in second-line was assumed to be 6.5 months. It was assumed that 40% and 60% of trial patients would be first-line and second-line patients, respectively. The median PFS in the control group (fulvestrant+ placebo) was estimated via simulation to be around nine months.

[b] The sponsor funded the trial and oversaw conduct of MONALEESA-3.

Source: Slamon 2020[4]

a) Trials

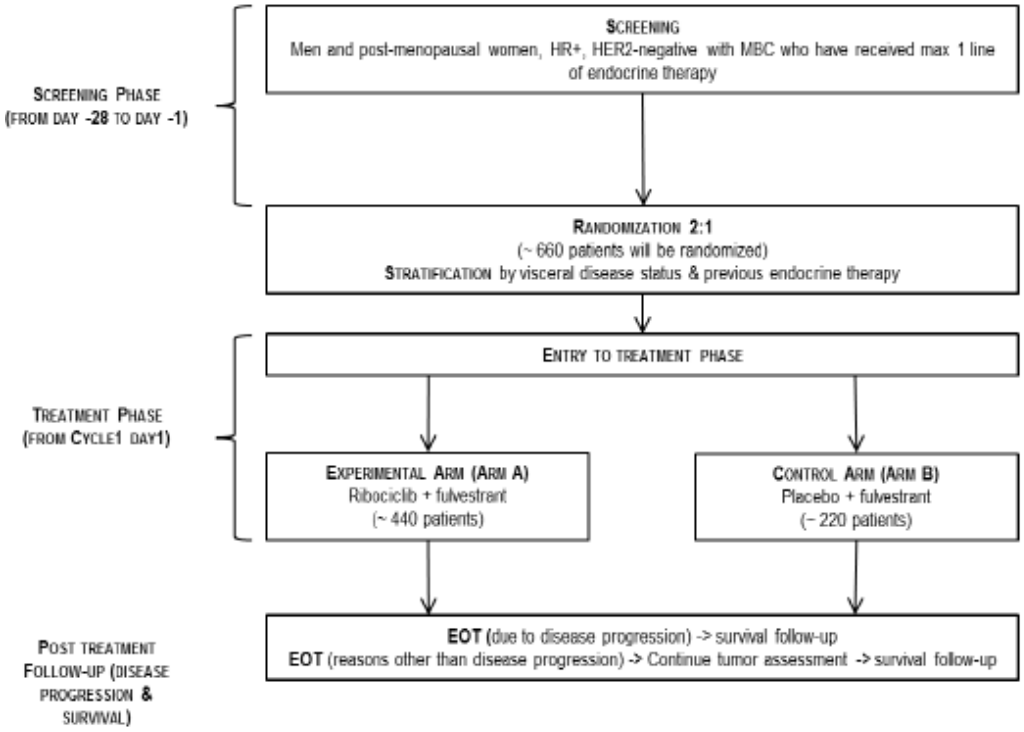
MONALEESA-3 is a phase 3, multi-centre, double-blind, placebo-controlled trial that was funded by the sponsor, Novartis Pharmaceuticals, who oversaw the conduct of the trial. A total of 726 post-menopausal patients with HR-positive, HER2-negative ABC were randomized in a 2:1 manner to either ribociclib or placebo, both on a background of fulvestrant. Patients in the intervention group received ribociclib 600 mg orally once daily for days 1 to 21 of a 28-day cycle and fulvestrant 500 mg intramuscularly on day 1 of each cycle with an additional injection on day 15 of cycle 1. Patients in the control group received placebo matched to ribociclib to maintain blinding. Figure 6.2 depicts the design of the MONALEESA-3 trial.

Randomization was stratified by presence of lung or liver metastases (yes/no), and previous ET, and patients were classified based on the following criteria:

- Group A – first-line treatment (endocrine sensitive): patients whose disease relapsed more than 12 months after completion of (neo)adjuvant ET with no subsequent treatment for ABC, or patients with do novo ABC (no prior exposure to ET);

- Group B – second-line treatment or early relapse (endocrine resistant): patients who received up to one line of treatment for ABC, and:
    i. whose disease relapsed on or within 12 months from completion of (neo)adjuvant ET, with no subsequent treatment for ABC; or
    ii. relapsed more than 12 months after completion of (neo)adjuvant ET, and progressed on or after subsequent ET for ABC; or
    iii. had ABC at time of diagnosis that progressed on or after ET for ABC with no prior (neo) adjuvant therapy for early disease.

Figure 6.2: Trial design of MONALEESA-3



Source: From The New England Journal of Medicine, Slamon DJ et al, Overall survival with ribociclib plus fulvestrant in advanced breast cancer, 382, pg. 514-24. Copyright ©2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. [4]

Outcomes and Statistical Analyses

Tumour response was assessed according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 at screening, and every eight weeks after randomization for 18 months, and every 12 weeks thereafter until disease progression, death, withdrawn consent or loss to follow up. Imaging from approximately 40% of randomly selected patients was reviewed by BIRC, and these results were also presented.

Primary Outcome – Investigator Assessed PFS

The primary outcome of MONALEESA-3 was locally assessed PFS, which was defined as the time from the date of randomization to the date of the first documented

progression or death due to any cause. The primary efficacy analysis of PFS was to be carried out once 125 PFS events had occurred in treatment naïve patients or after a total of 364 events was observed. Based on the estimated median PFS and proportion of patients receiving first-line and second line therapy, respectively, it was expected that the accumulation of events in first-line patients would be slower than in second-line patients. To ensure sufficient data were obtained from first-line patients, the final analysis was planned to be conducted once approximately 125 events occurred in first-line patients or approximately 364 events occurred in both treatment groups, whichever came later.[3]

The primary analysis was carried out using a stratified long-rank test at a one-sided 2.5% level of significance. The BIRC assessment of PFS was analyzed using a Cox proportional hazards model. PFS was censored if no PFS event had occurred before the data cut-off date; and the censoring date was the date of the last adequate tumour assessment prior to the data cut-off date. 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.[4]

Subgroup analyses were conducted if the primary analysis was found to be statistically significant. These analyses were performed at the level of the stratification factors and included Kaplan-Meier summaries and estimation of HRs from un-stratified Cox regression. Additional subgroup analyses based on demographics and disease-related baseline characteristics were also performed to determine heterogeneity of the treatment effect.[4]

Secondary Outcomes

OS was a secondary endpoint, and multiplicity was accounted for by the use of a hierarchical testing procedure, whereby this outcome was only to be tested if statistical significance was found for the primary outcome. OS was tested using a stratified log rank test at a one-sided alpha of 2.5%. Three interim analyses were planned for OS; one at the time of the PFS assessment (161 deaths anticipated at this time), after 263 deaths, and after 351 deaths. The type 1 error rate was controlled using a 3-look sequential design with Lan-DeMets alpha spending function. It was hypothesized that the addition of ribociclib to fulvestrant would result in a 29% reduction (HR=0.71) in the hazard rate for OS (corresponding to an increase in median survival to 42 months).

Additional secondary outcomes were assessed but not included in the statistical hierarchy and included ORR (confirmed CR or PR), TTR (time from randomization to first documented CR or PR), and DOR (time from first documented CR or PR 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 supportive analysis, these tests were also performed on the subset of patients with measurable disease.

Time-to-10% deterioration in global health status/QOL scale score on the EORTC QLQ C30 was the primary patient-reported outcome of interest, while emotional, physical and social function subscales, the BPI-SF worst pain item, pain severity index, pain interference subscales, and the EQ-5D—5L were also assessed but were of secondary interest. No formal statistical tests for any 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 MCID was specified for any of the HRQOL assessment instruments.[4]

The EORTC-QLQ-C30 contains 30 items, including global health status/QOL, 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).[4] 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 the 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. Higher scores on the EQ-5D-5L indicate better health status. The BPI-SF is an 11-item self-administered questionnaire that evaluates the intensity and impairment caused by cancer pain. Four questions measure pain intensity (pain now, average pain, worst pain and least pain) and are rated on a scale from 0 ('no pain') to 10 ('pain as bad as you can imagine'). An additional seven questions measure the level of interference caused by pain (general activity, mood, walking ability, normal work, relations with other persons, sleep and enjoyment of life) using a scale from 0 (no interference) to 10 (complete interference). The results from the BPI-SF were aggregated into a pain severity index that is based on the sum of the four pain intensity items and pain interference indices defined as subscale scores of pain interference with activity (interference with walking, general activity and work) and affect (relations with others, enjoyment of life and mood). HRQOL was assessed at screening, every eight weeks after randomization for the first 18 months and every 12 weeks until 36 months. Thereafter, data collection aligned with periodic efficacy assessments until disease progression, death, withdrawn consent, loss to follow-up, or patient/guardian decision, and at the end of therapy visit.

Protocol Amendments

There were two trial protocol amendments.[3] The first amendment occurred in February 2016 after 351 patients had been enrolled and involved a modification to the eligibility criteria to include males. The second protocol amendment included four changes and occurred in July 2016 after 727 patients had been enrolled: the futility interim analysis of the primary outcome was eliminated; the planned efficacy interim analysis was also eliminated and a requirement for a minimum number of events in first-line patients for the final analysis was added. Assessment of PFS based on BICR was not a secondary outcome but was added as a supportive analysis, and progression on next-line therapy was added as an exploratory analysis.

Adverse events were graded using the Common Terminology Criteria for Adverse Events version 4.03. The analysis of safety was done throughout the trial until 30 days after patients' last dose of study medication. 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, and as clinically indicated.

The outcomes of patients who moved on to subsequent therapy after discontinuing treatment in MONALEESA-3 were tracked under the exploratory outcome of PFS2. PFS2 was defined as the time from randomization to disease progression or death from any cause on the first new subsequent systemic therapy for those patients who had discontinued study treatment.[4]

b) Populations

MONALEESA-3 enrolled a total of 726 patients, 484 into the ribociclib group and 242 into the placebo group. Enrolled patients had a median age of 63 years of age, all were female, and 85% were Caucasian. Males were eligible to be enrolled in the trial, but none were recruited. There were 12 patients enrolled at Canadian sites.[3]

The baseline demographic and clinical characteristics were balanced between the two treatment groups. Overall, about two thirds (65%) of patients had an ECOG performance status of 0, while the remainder had a status of 1. At trial entry, almost all patients (99%) had stage IV disease. Approximately 60% of patients had visceral metastases and approximately 21% had bone metastases only. The majority of patients (78%) had more than 12 months elapse since their initial diagnosis of primary breast cancer. Approximately 19% had de novo disease.

The majority of patients had prior ET. In the ribociclib group approximately 49% of patients received up to one prior line of ET compared to 45% in the placebo group. Approximately 49% of patients were treatment naïve for ABC in the ribociclib group compared to 53% in the placebo group.

Table 6.4: Baseline characteristics of patients in the MONALEESA-3 trial

Table 1. Demographics and Baseline Characteristics

Characteristic	Ribociclib + Fulvestrant (n = 484), No. (%)	Placebo + Fulvestrant (n = 242), No. (%)
Gender		
Female	484 (100)	242 (100)
Age, year		
Median	63.0	63.0
Range	31–89	34–86
Race		
White	406 (83.9)	213 (88.0)
Asian	45 (9.3)	18 (7.4)
Native American	5 (1.0)	1 (0.4)
Black	3 (0.6)	2 (0.8)
Unknown	15 (3.1)	5 (2.1)
Other	10 (2.1)	3 (1.2)
ECOG PS		
0	310 (64.0)	158 (65.3)
1	173 (35.7)	83 (34.3)
Missing	1 (0.2)	1 (0.4)
Disease stage at study entry		
II	2 (0.4)	0 (0.0)
III	4 (0.8)	2 (0.8)
IV	478 (98.8)	239 (98.8)
Missing	0 (0.0)	1 (0.4)
Hormone receptor status		
ER positive	481 (99.4)	241 (99.6)
PR positive	353 (72.9)	167 (69.0)
Disease-free interval, months*		
De novo	97 (20.0)	42 (17.4)
Non-de novo	387 (80.0)	199 (82.2)
≤12	22 (4.5)	9 (3.7)
>12	365 (75.4)	190 (78.5)
Missing	0 (0.0)	1 (0.4)
Prior endocrine therapy status†		
Treatment naive	238 (49.2)	129 (53.3)
Up to one line of endocrine therapy	236 (48.8)	109 (45.0)
Prior endocrine therapy setting		
(Neo)adjuvant	289 (59.7)	142 (58.7)
Advanced	110 (22.7)	40 (16.5)
Prior chemotherapy		
Adjuvant	209 (43.2)	101 (41.7)
Neoadjuvant	65 (13.4)	30 (12.4)
Metastatic sites		
0	2 (0.4)	0 (0.0)
1	151 (31.2)	73 (30.2)
2	156 (32.2)	76 (31.4)
3	114 (23.6)	48 (19.8)
4	38 (7.9)	34 (14.0)
≥5	23 (4.8)	10 (4.1)
Missing	0 (0.0)	1 (0.4)
Sites of metastases		
Bone	367 (75.8)	180 (74.4)
Bone only	103 (21.3)	51 (21.1)
Visceral	293 (60.5)	146 (60.3)
Lung	146 (30.2)	72 (29.8)
Liver	134 (27.7)	63 (26.0)
Lung or liver	242 (50.0)	121 (50.0)
Central nervous system	6 (1.2)	2 (0.8)
Other‡	102 (21.1)	51 (21.1)
Lymph nodes	199 (41.1)	115 (47.5)
Soft tissue	23 (4.8)	14 (5.8)
Skin	20 (4.1)	8 (3.3)
Breast	4 (0.8)	1 (0.4)
None	2 (0.4)	0 (0.0)
Missing	0 (0.0)	1 (0.4)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; PR, progesterone receptor.
*De novo includes patients with no first recurrence/progression or with a first recurrence/progression within 90 days of diagnosis with no prior medication. For non-de novo disease, disease-free interval is defined as the time from initial diagnosis to first recurrence/progression.
†Fourteen patients not included because of missing data or criteria not being met.
‡Other visceral sites include metastatic site other than soft tissue, breast, bone, lung, liver, central nervous system, skin, and lymph nodes.

Source: Reprinted with permission. ©2018 American Society of Clinical Oncology. All rights reserved. Slamon DJ et al: J Clin Oncol Vol. 36(24), 2018: 2465-2472.[2]

c) Interventions

MONALEESA-3 compared ribociclib at a dose of 600 mg orally once daily, for days 1 to 21 of a 28-day cycle, to matched placebo. All patients received fulvestrant 500 mg by intramuscular injection on days 1 and 15, and monthly thereafter. Treatment continued until patients experienced disease progression, unacceptable toxicity, death, or discontinuation for any other reason. Dose modifications to ribociclib were allowed to manage adverse events, including up to two dose reductions, or dose interruption. Dose modifications to fulvestrant were not allowed.

Dose reductions occurred in 38% (n=183) of patients in the ribociclib plus fulvestrant group and 4% (n=10) in the placebo plus fulvestrant group. With ribociclib plus fulvestrant, 33% of patients had a single dose reduction, versus 4% with placebo plus fulvestrant.

At the primary analysis the median duration of treatment exposure in the ribociclib group was 15.8 months (range, 0.9 to 27.4) compared to 12 months (range, 0.9 to 25.9) in the placebo group. The median relative dose intensity for the ribociclib plus fulvestrant versus placebo plus fulvestrant treatment groups was 92.1% and 100%, respectively.

The percentage of patients receiving subsequent anti-neoplastic therapy was 82% (n=295) in the ribociclib plus fulvestrant group and 85% (n=177) in the placebo plus fulvestrant group.[4] Chemotherapy alone or in combination was the subsequent therapy in 36% (n=130) of patients in the ribociclib plus fulvestrant group and 36% (n=75) of patients with placebo plus fulvestrant. Hormone therapy alone was taken as subsequent therapy by 26% (94 patients) of ribociclib plus fulvestrant patients and 18% (38 patients) of placebo plus fulvestrant patients, and hormone therapy plus other was taken in 18% (66 patients) and 29% (61 patients) of patients in each group, respectively. In the ribociclib group, 11% (40 patients) of patients went on to take a subsequent CDK 4/6 inhibitor compared to 25% (53 patients) with placebo.

Drugs required to manage adverse events, cancer symptoms, concurrent diseases, and supportive care such as pain medications, anti-emetics, and anti-diarrheals were permitted.[4] Patients on a chronic regimen could try to maintain the same dose and regimen throughout the study, where medically feasible. 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 CYP 450 isozymes, as well as other drugs that may cause issues with drug interactions or increase risk of QT prolongation.

d) Patient Disposition

At the cut-off date for the primary efficacy analysis (November 3, 2017), the median follow-up of patients was 20.4 months. At this time, 58% of patients in the ribociclib group and 68% in the placebo group had discontinued treatment. The most common reason for discontinuing treatment in both the ribociclib and placebo groups was progressive disease (40% versus 59% of patients, respectively).

The full analysis set (FAS) included all randomized patients, and this was the population that was the focus off efficacy analyses. An intent-to-treat (ITT) analysis was performed; patients were to be analyzed according to the

treatment/stratum assigned at randomization. Safety analyses were based on the safety analysis set (SAS), which included all patients receiving at least one dose of study medication and had at least one post-baseline safety assessment.

There was a total of 16 patients who had a protocol deviation that resulted in exclusion from the per protocol set (PPS), which included 11 (2%) ribociclib-treated patients and 5 (2%) placebo patients.[3] These deviations were all due to selection criteria not being met, with the most common deficiency being that they failed to meet criteria for measurable disease or lytic bone lesion.

Table 6.5: Patient disposition in the MONALEESA-3 trial

Patient Disposition	MONALEESA-3	
	Ribociclib N=483	Placebo N=241
Screened, N	971	
Randomized, n (%)	484	242
Randomized and treated, n (%)	483	241
Data cut-off Date – November 3, 2017 (median follow-up of 20.4 months)		
Discontinued treatment, n (%)	279 (58)	165 (68)
Reason for end of treatment, n (%)		
-progressive disease	193 (40)	142 (59)
-adverse event	41 (9)	10 (4)
-physician decision	22 (5)	7 (3)
-patient/guardian decision	21 (4)	5 (2)
-death	2 (<1)	0
-protocol deviation	1 (<1)	1 (<1)
-technical problems	0	1 (<1)
Data cut-off Date – June 3, 2019 (median follow-up of 39.4 months)		
Treatment ongoing, n (%)	121 (25)	32 (13)
Discontinued treatment	362 (75)	209 (86)
Reason for end of treatment		
-Progressive disease	263 (54)	184 (76)
-Adverse event	43 (9)	9 (4)
-Physician decision	28 (6)	8 (3)
-Patient/guardian decision	26 (5)	6 (3)
-Death	2 (<1)	1 (<1)
-Protocol deviation	1 (<1)	1 (<1)
-Technical issue	0	1 (<1)
Full analysis set, N	484 (100)	242 (100)
Safety analysis set, N	483 (>99)	241 (>99)
Source: Slamon 2018;[2] Slamon 2020[4]		

e) Limitations/Sources of Bias

Overall, MONALEESA-3 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, and neither have been directly compared to ribociclib. 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. Due to the lack of an active comparator, the sponsor provided an ITC that compared ribociclib plus fulvestrant to active comparators. The ITC is summarized in Section 7 of this report.

MONALEESA-3 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 may have alerted investigators and patients to identity of 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 the 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 HRQOL analyses. Namely, although baseline data were available for 99% of patients, end of treatment data were only available for less than half of the original ITT population. A large amount of missing data introduces significant potential for confounding and selection bias. For example, the remaining patients sampled 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.

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

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The primary efficacy analysis was performed on November 3, 2017, at which point median follow-up of trial patients was 20.4 months. Efficacy outcomes of the MONALEESA-3 trial are summarized in Table 6.6.

Table 6.6: Efficacy outcomes in the MONALEESA-3 trial.

Efficacy Outcomes	MONALEESA-3	
	Ribociclib N=483	Placebo N=241
PROGRESSION-FREE SURVIVAL		
*Primary efficacy analysis**		
Median PFS, months (95% CI)	20.5 (18.5, 23.5)	12.8 (10.9, 16.3)
Number of events - n (%)	210 (43.4)	151 (62.4)
-Progression	200 (41.3)	143 (59.1)
-Death	10 (2.1)	8 (3.3)
-Censored	274 (56.6)	91 (37.6)
HR (95% CI);[a] p-value	0.59 (0.48, 0.73); p<0.001	
*BIRC assessment**	N=193	N=97
HR (95% CI)[a]	0.49 (0.35 to 0.70)	
*Updated (exploratory) PFS***		
Median PFS, months (95% CI),	20.6 (not reported)	12.8 (not reported)
HR (95% CI)[a]	0.59 (0.49, 0.71)	
OVERALL SURVIVAL		
*1st interim analysis**		
Number of events – n (%)	70 (14.5)	50 (20.7)
HR (95% CI); p-value	0.67 (0.47, 0.96); p=0.015	
*2nd interim analysis***		
Number of events – n (%)	167 (34.5)	108 (44.6)
Median OS (95% CI), months	Not reached	40.0 (37.0, NE)
HR (95% CI);[b] p-value	0.72 (0.57, 0.92); p=0.00455	
OVERALL RESPONSE		
*All patients**		
CR, n (%)	8 (2)	0
PR	149 (31)	52 (22)
SD	161 (33)	83 (34)
Non-CR/Non-PD	88 (18)	54 (22)
PD	48 (10)	40 (17)
Unknown	30 (6)	13 (5)
ORR, n (%) [95% CI]	157 (32) [28 to 37]	52 (22) [16 to 27]
*Patients with measurable disease**	N=379	N=181
CR, n (%)	6 (2)	0
PR	149 (39)	52 (29)
SD	161 (43)	83 (46)
PD	40 (11)	35 (19)
Unknown	23 (6)	11 (6)
ORR, n (%) [95% CI]	155 (41) [36 to 46]	52 (29) [22 to 35]
TIME-TO RESPONSE		
Median time-to-response	Not reached	Not reached
DURATION OF RESPONSE		
Median DOR	Not reached	Not reached
TIME-TO CHEMOTHERAPY		
Receipt of first chemotherapy, HR (95% CI)**	0.70 (95% CI: 0.55, 0.88)	

Abbreviations: BIRC=blinded independent radiology committee; CI = confidence interval; CR=complete response; DOR=duration of response; HR=hazard ratio; NE=not estimable; OR = odds ratio; ORR – objective response rate; OS – overall survival; PFS=progression-free survival; PD=progressive disease; PR=partial response.

Notes:

[a] One-sided p-value obtained from stratified log-rank test. HR obtained from Cox proportional hazards model stratified by liver and/or lung metastases and previous endocrine therapy as per interactive response technology (IRT).

[b] 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:
*November 3, 2017: 20.4 months
**June 3, 2019: 39.4 months

Sources: FDA Clinical Review;[5] Slamon 2018;[2] Slamon 2020[4]

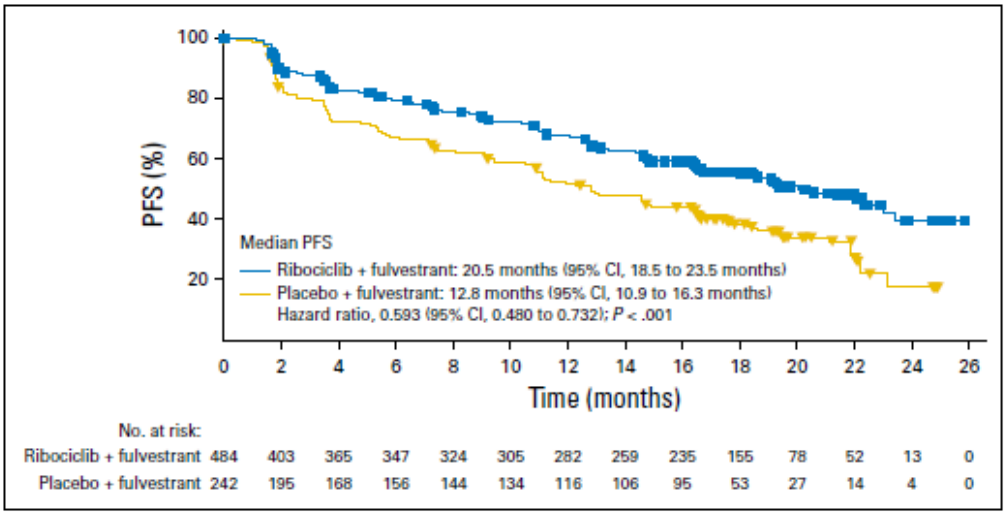
Efficacy Outcomes

Primary Outcome - Progression-free Survival by Investigator Assessment -

As of the data cut-off date (November 3, 2017), there were 361 progression events in total, with fewer progression events observed in the ribociclib group versus the placebo group (n=151; 62% of patients) for a statistically significant difference between groups (HR of 0.59 [95% CI: 0.48, 0.73]; p<0.0001; Figure 6.3). The median PFS by investigator assessment was 20.5 months (95% CI: 18.5, 23.5) in the ribociclib group compared to 12.8 months (95% CI: 10.9, 16.3) in the placebo group. Results from the BIRC assessment were consistent with those of the primary analysis (HR of 0.49 [95% CI: 0.35 to 0.70]).

With respect to subgroup analyses of PFS (Figure 6.4), the treatment effect appeared consistent across all patient subgroups (HRs ranging from 0.38 to 0.67) with the exception of Asian and Other race, which are groups limited by small sample size and event rates. There were no clear between-group differences in PFS based on previous ET, whether patients were treatment naive (HR of 0.58 [95% CI: 0.42, 0.80]) or had up to one previous line of ET (HR of 0.57 [95% CI: 0.43, 0.74]), or prior tamoxifen use (HR of 0.62 [95% CI: 0.44, 0.87]; [95% CI: 0.43, 0.74]) or prior AI use (HR of 0.67 [95% CI: 0.51, 0.89];). As no tests for interaction were performed and these analyses were not controlled for multiplicity, these analyses should be considered exploratory and interpreted accordingly.

Figure 6.3: Kaplan-Meier analysis of PFS (investigator assessment) in MONALEESA-3



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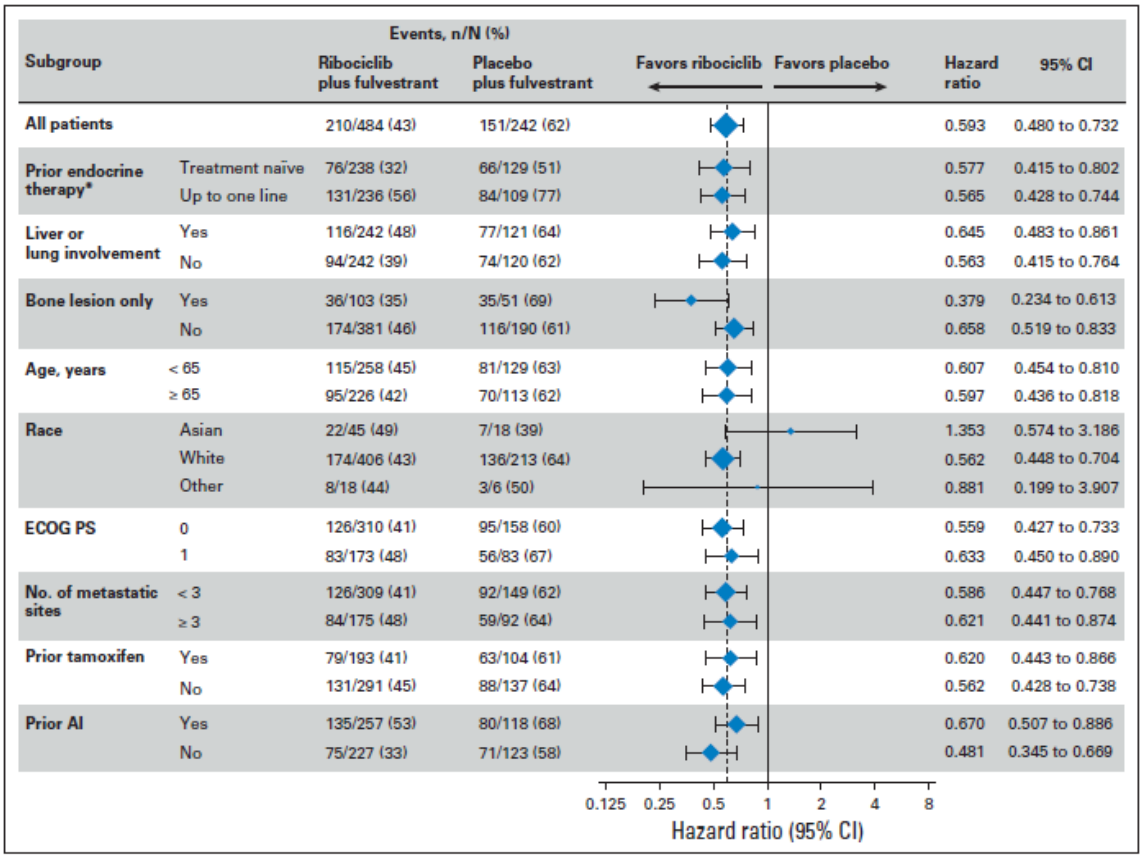
An updated (exploratory) analysis of PFS was performed at the time of the final OS analysis, with a data cutoff of June 3, 2019. The updated PFS was consistent with that of the primary analysis, with a median PFS of 20.6 months in the ribociclib group and 12.8 months in the placebo group, for a HR of 0.59 (95% CI: 0.49, 0.71).[4] In patients receiving first-line therapy, the median PFS for ribociclib plus fulvestrant was 33.6 months and for placebo plus fulvestrant was 19.2 months, for a HR of 0.55 (95% CI: 0.42, 0.72). For those with early relapse or receiving second line treatment, the median PFS was 14.6 months with ribociclib plus fulvestrant and 9.1 months with placebo plus fulvestrant, for a HR of 0.57 (95% CI: 0.44, 0.74).[4]

The outcomes of patients who moved on to subsequent therapy after discontinuing treatment in MONALEESA-3 were documented under the exploratory outcome PFS2. There were 45% (n=217) of patients in the ribociclib group and 58% (n=141) of patients in the placebo group who had a PFS2 event. The median PFS2 was longer with patients in the ribociclib plus fulvestrant (39.8 months) compared to those in the placebo plus fulvestrant group (29.4 months) for a HR of 0.67 (95% CI: 0.54, 0.83).[4]

Figure 6.4: Subgroup analyses of investigator-assessed PFS in the MONALEESA-3 trial



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Secondary Outcomes

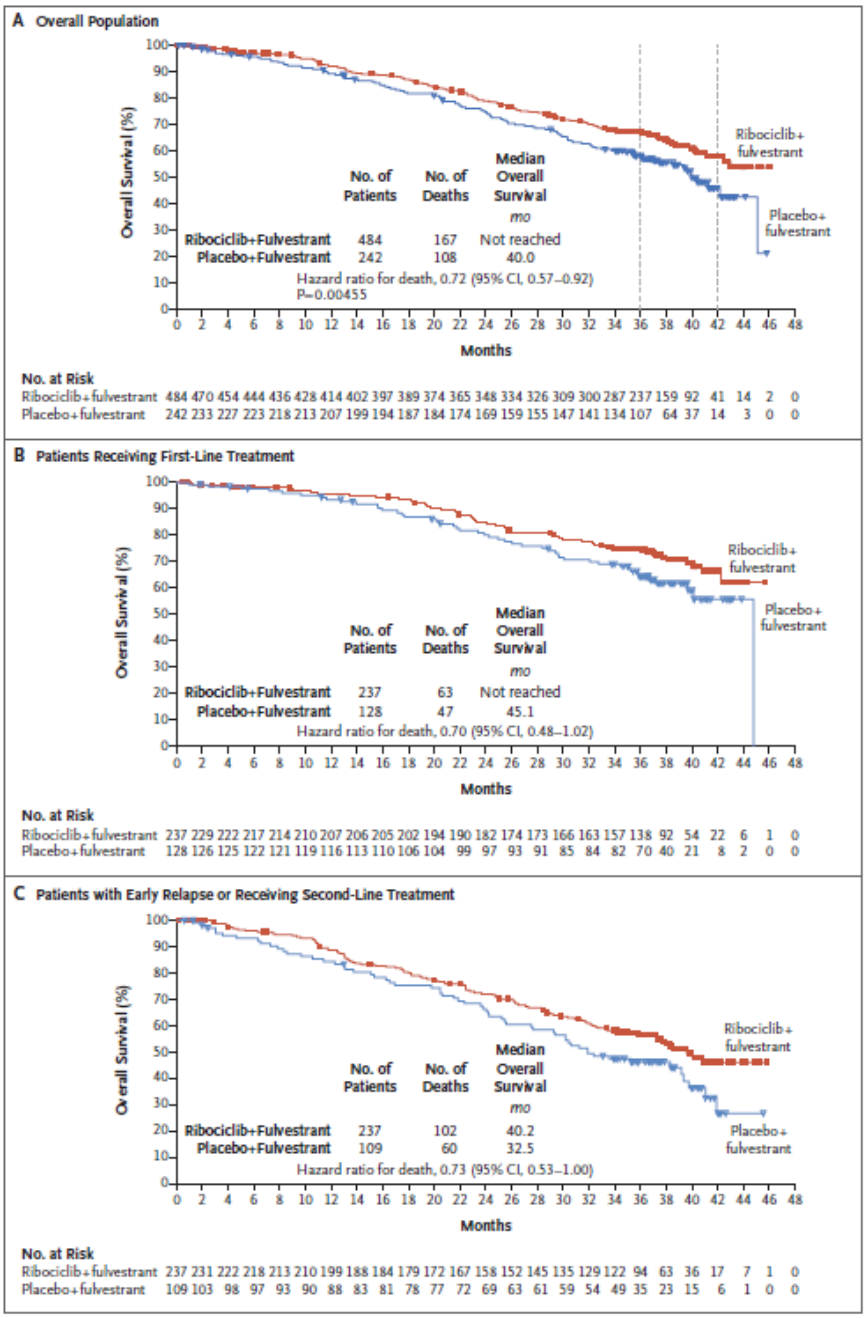
Key Secondary Outcome – Overall Survival

There was no statistically significant difference in OS between the treatment groups, as of the primary analysis data cut-off date, with 15% (n=70) of patients in the ribociclib group and 21% (n=20) of patients in the placebo with an event of death at this time point. However, by the time of the pre-planned second interim analysis, there was a total of 275 deaths, with 35% (n=167) of patients in the ribociclib group and 45% (n=108) of patients in the placebo group with an event of death (HR of 0.72 [95% CI: 0.57, 0.92]; p=0.00455). 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<0.01129, and therefore it was considered the final analysis of OS. The median OS was not reached in the ribociclib group and was 40.0 months (95% CI: 37.0, not estimable) in the placebo group.

In pre-specified subgroup analyses of OS, the treatment effect remained consistent based on line of therapy. In patients who received treatment in first-line, 27% (n=63) of patients in the ribociclib group and 37% of patients in the placebo group had an event of death for a HR of 0.70 [95% CI: 0.48, 1.02]); and in patients who

received treatment for early relapse or in second-line, 43% (n=102) of patients in the ribociclib group and 55% (n=60) in the placebo group had an event of death for a HR of 0.73 [95% CI: 0.53, 1.00]).

Figure 6.5: Kaplan-Meier analysis of OS (final analysis) in the MONALEESA-3 trial (A: overall patient population; B: patients receiving trial treatment as first-line therapy; and C: patients receiving trial treatment for early relapse or as second-line therapy)



Source: From The New England Journal of Medicine, Slamon DJ et al, Overall survival with ribociclib plus fulvestrant in advanced breast cancer, 382, pg. 514-24. Copyright ©2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[4]

Objective Response

In the FAS (ITT) population, the ORR was 32% (95% CI: 28%, 37%) in the ribociclib group and 22% (95% CI: 16%, 27%) in the placebo group. A CR occurred in 2% of patients who received ribociclib and none of those who received placebo; a PR occurred in 31% and 22% of patients in the ribociclib and placebo groups, respectively. In patients with measurable disease at baseline, the ORR was 41% (95% CI: 36%, 46%) and 29% (95% CI: 22%, 35%) in the ribociclib and placebo groups, respectively. A CR occurred in 2% of patients in the ribociclib group and none of those in the placebo group; a PR occurred in 39% and 29% of patients in the ribociclib and placebo groups, respectively (refer to Table 6.6).

Time-to-Objective Response

The median time-to-response was not reached in either the ribociclib or placebo group (Table 6.6).

Duration of Response

The median DOR was not reached in either the ribociclib or placebo group (Table 6.6).

Time-to-Chemotherapy

The median time-to-first chemotherapy was not reached in the ribociclib group and was 29.5 months with placebo, for a HR for receipt of first chemotherapy of 0.70 (95% CI: 0.55, 0.88).[4]

Health-related Quality of Life

As previously mentioned, changes in HRQOL were expressed as time-to-10% deterioration in subscales of the EORTC-QLQ-C30. A definitive 10% deterioration was defined as a worsening of 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 of HRQOL endpoints were performed. Baseline assessments for the EORTC-QLQ-C30 were obtained from 93% of patients in MONALEESA-3; however, by the time end of treatment assessments were performed, data were only available from 41% of patients.[6] The median time-to-definitive 10% deterioration in global health status/QOL, the primary patient-reported outcome of interest, was not reached for the ribociclib plus fulvestrant group and was 19.4 months in the placebo plus fulvestrant group. The HR for deterioration in global health status/QOL was 0.80 (95% CI: 0.60, 1.05). The HR for time-to-deterioration for the various QLQ-C30 subscales numerically favoured ribociclib plus fulvestrant but the CIs indicated no difference between the treatment groups (Table 6.7). The same was observed for time-to-deterioration in the pain subscales of the BPI-SF and the EQ-5D-5L VAS.

Table 6.7: HRQOL outcomes in the MONALEESA-3 trial

HRQOL Outcomes	MONALEESA-3	
	Ribociclib N=483	Placebo N=241
HEALTH-RELATED QUALITY OF LIFE		
EORTC-QLQ-C30: Global Health Status		
Mean (SD) baseline	65.5 (NR) N=445	68.4 (NR) N=225
Mean (SD) change from baseline to end of therapy	-5.2 (NR) N=184	-5.5 (NR) N=113
LSM change from baseline (95% CI)	-6.2 (NR)	-4.2 (NR)
Treatment difference (95% CI)	-2.0 (NR)	
Median time to 10% deterioration in global health status/QOL scale score of EORTC QLQ-C30	Not reached	19.4 months
HR (95% CI)	0.80 (0.60, 1.05)	
Other Subscales:		
Median time-to-10% deterioration in physical functioning scale score of EORTC QLQ-C30 HR (95% CI)	Numerical results not reported, but 'no meaningful difference observed'	
Median time-to-10% deterioration in emotional functioning scale score of EORTC QLQ-C30 HR (95% CI)	Numerical results not reported, but 'no meaningful difference observed'	
Median time-to-10% deterioration in social functioning scale score of EORTC QLQ-C30 HR (95% CI)	Numerical results not reported, but 'no meaningful difference observed'	
Time-to-deterioration in BPI-SF worst pain HR (95% CI)	0.81 (0.58, 1.13)	
Time-to-deterioration in BPI-SF pain severity index HR (95% CI)	0.81 (0.60, 1.11)	
Time-to-deterioration in BPI-SF pain interference index HR (95% CI)	0.87 (0.63, 1.21)	
Time-to-10% deterioration EQ-5D-5L VAS HR ratio (95% CI)	0.87 (0.66, 1.16)	

Abbreviations: BPI-SF=brief pain inventory, short form; CI = confidence interval; EORTC QLQ-C30= European Organization for the Research and Treatment of Cancer, Quality of Life Questionnaire; HR=hazard ratio; LSM=least square mean; NR=not reported; QOL=quality of life; SD=standard deviation.

Sources: Slamon 2018,[2] FDA Clinical Review[5], Checkpoint response[6]

Harms Outcomes

Adverse Events

Adverse events (all grades) occurred in 99% of patients in the ribociclib group and 96% of patients in the placebo group (Table 6.8). Grade 3 or 4 adverse events occurred in 78% of patients treated with ribociclib and 30% of patients treated with placebo; the most common adverse event was neutropenia, which occurred in 70% of ribociclib- and 2% of placebo-treated patients. Other cytopenias also occurred with greater frequency in patients treated with ribociclib compared to those in the placebo group including anemia (17% versus 5%) and leukopenia (28% versus 2%). Other adverse events where there was a 10% difference between groups included nausea (45% versus 28%) and vomiting (27% versus 13%), constipation (25% versus 12%) and alopecia (19% versus 5%). Adverse events were the most common reason

for dose reduction, and 33% of patients in the ribociclib group had at least one dose reduction versus 3% in the placebo group.

Serious Adverse Events

Serious adverse events were reported in 29% of patients treated with ribociclib compared to 17% of placebo-treated patients (Table 6.8). Of these, 11% of events in the ribociclib group and 3% in the placebo group were attributed to the study medication. The most common serious adverse event was pneumonia, which occurred in 2% of patients receiving ribociclib and no patients in the placebo group, and dyspnea which occurred in 1% and 2% of ribociclib and placebo patients, respectively.

There were 13 deaths (2.7%) in the ribociclib group and eight deaths (3.3%) in the placebo group during treatment or within 30 days of discontinuing treatment (Table 6.8). Most of the deaths (seven in each group) were due to disease progression. There was one death in the ribociclib group that was suspected to be related to study treatment; this patient died from acute respiratory distress syndrome and had baseline lung metastases. The remaining five deaths were not considered to be related to treatment.

Withdrawal due to Adverse Events

Withdrawal due to an adverse event occurred more frequently in the ribociclib-treated patients at 17%, compared to 6% of patients in the placebo group (Table 6.8), and were primarily attributable to increases in ALT or AST.[5]

Notable Harms

Neutropenia was a notable harm and as noted previously was the most common adverse event with ribociclib. Grade 4 neutropenia occurred in 7% of ribociclib patients versus none with placebo (Table 6.8). Pneumonia was the most common serious adverse event in the ribociclib group, occurring in 2% of patients versus in no patients treated with placebo. QT prolongation was another notable harm, and prolongation of >60 ms occurred in 7% of patients in the ribociclib group versus <1% of patients in the placebo group. There were three patients (0.6%) in the ribociclib group and no patients in the placebo group who discontinued study treatment because of a prolonged QTcF interval. There were no cases of torsades de pointes in the trial. Fatigue occurred in similar proportions of patients between groups (ribociclib: 32%; placebo: 33%). Hepatic events in the form of grade 3 elevations in ALT were noted in 7% of ribociclib-treated patients compared to 2% in placebo-treated patients. There were two patients in the ribociclib group with confirmed cases of Hy's law, and their liver enzymes returned to normal after discontinuation of ribociclib.

Table 6.8: Summary of harms in the MONALEESA-3 trial

Harms Outcomes	MONALEESA-3					
	Ribociclib N=483			Placebo N=241		
MEDIAN DURATION OF EXPOSURE	15.8 months			12.0 months		
ADVERSE EVENTS	All	Grade 3 and 4		All	Grade 3 and 4	
Patients with > 0 AEs, N (%)	479 (99)	378 (78)		231 (96)	71 (30)	
Most common adverse events, 10% in any group	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Neutropenia	336 (70)	225 (47)	33 (7)	5 (2)	0	0
Nausea	219 (45)	7 (1)	0	68 (28)	2 (1)	0
Fatigue	152 (32)	8 (2)	0	80 (33)	1 (<1)	0
Diarrhea	140 (29)	3 (1)	0	49 (20)	2 (1)	0
Leukopenia	137 (28)	65 (14)	3 (1)	4 (2)	0	0
Vomiting	129 (27)	7 (1)	0	31 (13)	0	0
Constipation	120 (25)	4 (1)	0	28 (12)	0	0
Arthralgia	116 (24)	3 (1)	0	64 (27)	1 (<1)	0
Cough	105 (22)	0	0	37 (15)	0	0
Headache	104 (22)	4 (1)	0	49 (20)	1 (<1)	0
Pruritus	96 (20)	1 (<1)	0	16 (7)	0	0
Alopecia	90 (19)	0	0	11 (5)	0	0
Rash	89 (18)	2 (<1)	0	14 (6)	0	0
Back pain	85 (18)	8 (2)	0	42 (17)	2 (1)	0
Anemia	83 (17)	15 (3)	0	13 (5)	5 (2)	0
Decreased appetite	78 (16)	1 (<1)	0	31 (13)	0	0
Pain in extremity	66 (14)	3 (1)	0	39 (16)	2 (1)	0
Hot flush	64 (13)	0	0	41 (17)	0	0
SERIOUS ADVERSE EVENTS						
Subjects with > 0 SAEs, N (%)	138 (29)			40 (17)		
Most common, 1% any group						
Pneumonia	9 (2)	8 (2)	0	0	0	0
Nausea	7 (1)	5 (1)	0	0	0	0
Vomiting	7 (1)	5 (1)	0	1 (<1)	0	0
Anemia	6 (1)	3 (1)	0	0	0	0
Dyspnea	6 (1)	5 (1)	0	5 (2)	4 (2)	0
Neutropenia	6 (1)	3 (1)	1 (<1)	0	0	0
Pleural effusion	6 (1)	4 (1)	1 (<1)	3 (1)	2 (1)	0
Abdominal pain	5 (1)	5 (1)	0	1 (<1)	1 (<1)	0
Acute kidney injury	5 (1)	4 (1)	0	0	0	0
Febrile neutropenia	5 (1)	5 (1)	0	0	0	0
Pyrexia	5 (1)	1 (<1)	0	1 (<1)	0	0
WDAEs						
WDAEs, N (%)	83 (17)	36 (8)	12 (3)	15 (6)	9 (4)	1 (<1)
Most common, 1% any group						
ALT increased	22 (5)	6 (1)	5 (1)	0	0	0
AST increased	13 (3)	3 (1)	3 (1)	1 (<1)	1 (<1)	0
Vomiting	5 (1)	1 (<1)	0	0	0	0
DEATHS						
Number of deaths, N (%)	13 (3)			8 (3)		
Most common reasons						
Disease progression	7 (1)			7 (3)		
Pulmonary embolism	1 (<1)			1 (<1)		
Acute respiratory distress syndrome	1 (<1)			0		
Cardiac failure	1 (<1)			0		
Pneumonia	1 (<1)			0		
Hemorrhagic shock	1 (<1)			0		
Ventricular arrhythmia	1 (<1)			0		

NOTABLE HARMS		
ECG QT prolongation, %	6.2	0.8
QTcF >480 msec post-baseline	5.6	2.5
QTcF >500 msec post-baseline	1.7	0.4
Increase from baseline QTcF >60ms	6.5	0.4
Elevated ALT, grade 3 or 4	32 (7)	9 (2)
Elevated AST	23 (5)	6 (1)
Febrile neutropenia	1%	0

Abbreviations: AE=adverse event; ALT=alanine Aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; msec=millseconds; NA=not applicable; WDAE= withdrawal due to adverse event; SAE=serious adverse event.

Notes:
Neutropenia includes neutropenia, decreased neutrophil count, febrile neutropenia, and neutropenic sepsis.
Leukopenia includes leukopenia, decreased white blood cell count, lymphopenia, and decreased lymphocyte count.
Anemia includes anemia, decreased hemoglobin level, and decreased red blood cell count.

Source: Slamon 2018;[2] EMA Assessment Report;[3] FDA Clinical Review[5]

An updated analysis of adverse events was performed at the time of the second interim analysis of OS (June 3, 2019), with a median follow up of 39.4 months.[4] The authors noted that adverse events were consistent with those seen at the primary analysis, and that there were no new safety signals. The most common grade 3 or 4 adverse events were neutropenia (57% with ribociclib, 1% with placebo) and leukopenia (16% with ribociclib and none with placebo). Other notable harms reported included grade 3 or 4 hepatobiliary toxic effects (14% in the ribociclib group versus 6% in the placebo group) and prolonged QT interval (3% with ribociclib, 1% with placebo). There was also one case of grade 3 or 4 interstitial lung disease in one ribociclib-treated patient (none in the placebo group).[4]

6.4 Ongoing Trials

One ongoing trial evaluating ribociclib plus fulvestrant in patients with HR-positive, HER2-negative ABC was identified and is summarized in Table 6.9. The final analysis of the MAINTAIN trial is expected in December 2021.

Table 6.9: Ongoing trials of ribociclib combined with fulvestrant in patients with HR-positive, HER2-negative ABC

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
MAINTAIN NCT02632045 Characteristics (Phase 2, double-blind, randomized) N= 132 11 sites: USA only Patient Enrolment Start Date: Mar 2016 Final Analysis Date: Dec 2021 Funding: Novartis Pharmaceuticals	Key Inclusion Criteria: • 18 years old • histologically or cytologically confirmed adenocarcinoma of the breast with unresectable or metastatic disease • HR+, HER2-, post-menopausal or receiving ovarian ablation, measurable disease • ECOG 0-1 Key Exclusion Criteria: • Prior use of SERD • Active CNS disease • CNS metastases allowed if clinically stable for ≥4 weeks after completion of definitive treatment • if active leptomeningeal disease, patient is ineligible • Visceral crisis • ≥1 prior systemic chemotherapy in unresectable or metastatic setting • Clinically significant uncontrolled heart disease and/or cardiac repolarization abnormality • Pregnant or nursing	**Intervention:** Ribociclib 600 mg daily (3 weeks on/1 week off), fulvestrant 500 mg IM injection every 2 weeks x 3, then every 4 weeks **Comparator:** Placebo daily (3 weeks on/1 week off), fulvestrant 500 mg IM injection every 2 weeks x 3, then every 4 weeks	Primary: PFS at 24 weeks Secondary: ORR
Abbreviations: CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; HER2- = human epidermal growth factor receptor negative; HR+ = hormone receptor positive; IM=intramuscular; ORR=objective response rate; PFS=progression-free survival; SERD=selective estrogen receptor down regulator. Source: clinicaltrals.gov;[57] Sponsor submission[54]			

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of ribociclib in combination with fulvestrant as initial treatment or following disease progression on ET in post-menopausal women with HR-positive, HER2-negative ABC:

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

7.1.1 Objective

As the MONALEESA-3 trial did not include a comparison to an active relevant comparator, the sponsor conducted an ITC to estimate the relative efficacy (PFS) and safety of ribociclib plus fulvestrant versus other treatments for patients with HR-positive, HER2-negative ABC.[58] The objective of the ITC was to provide inputs into the pharmacoeconomic model supporting this submission to evaluate the cost-effectiveness and budget impact of ribociclib plus fulvestrant for the indication under review. The ITC uses data from the MONALEESA-3 trial based on the most recent data cut-off date for PFS, which was June 3, 2019. At the request of pCODR, the sponsor updated the ITC to include other relevant CDK 4/6 inhibitors including palbociclib and abemaciclib plus AI.

7.1.2 Methods

Systematic Review

A systematic review of the literature was performed in April 2018 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, or 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 identified studies, there were 21 RCTs (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 sponsor conducted several ITCs, each with a different patient population derived from the MONALEESA-3 trial: the full trial population, Group A (ET sensitive: patients receiving first-line therapy, which excluded patients with a disease-free interval <12 months after (neo)adjuvant

therapy); Group B (ET resistant: first-line refractory and second-line patients); and Groups Bii and Biii combined (second-line patients).

The review focused on ribociclib plus fulvestrant, 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 for each of the aforementioned groups are summarized in Table 7.1. Comparators correspond to those identified as relevant within each subgroup for the economic evaluation and for which efficacy data in the subgroup could be identified. It should be noted that for the latter requirement, it was only required that the trial included some patients who were in the subgroup; these comparisons therefore should be interpreted cautiously to the extent that the trial populations do not match precisely across all trials included in each ITC.

Table 7.1. List of comparators in the ITC

Full population	Group A	Group B	Group Bii and Biii
• Fulvestrant • Palbociclib and fulvestrant • Abemaciclib and fulvestrant • Exemestane	• Fulvestrant • Letrozole • Exemestane • Palbociclib + fulvestrant • Ribociclib + AI • Palbociclib +AI • Abemaciclib +AI	• Fulvestrant • Exemestane • Tamoxifen • Palbociclib + fulvestrant • Abemaciclib + fulvestrant • Everolimus + exemestane	• Fulvestrant • Exemestane • Tamoxifen • Palbociclib + fulvestrant • Abemaciclib + fulvestrant • Everolimus + exemestane

Source: ITC report[58]

Chemotherapy was not included as a comparator because its use would typically be limited to patients with rapidly progressing and/or life-threatening disease.

The primary outcome of interest to the ITC was PFS, while adverse events were a secondary measure of interest. It was noted OS and ORR were not measures of interest as these outcomes were not required for the pharmacoeconomic model.

Quality assessment of 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 of PFS 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.

For the analysis of adverse events only events grade ≥3 or greater with an incidence of at least 5% for any comparator of interest were included. 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-3 trial was used to estimate the incidence of all-cause grade 3 or higher adverse events for ribociclib plus fulvestrant and fulvestrant monotherapy.

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 16 trials were included in the ITCs (refer to Table 7.2), which evaluated CDK 4/6 inhibitors (ribociclib, palbociclib, and abemaciclib), AI, fulvestrant, tamoxifen, and everolimus with or without exemestane. In some trials like MONALEESA-3, multiple populations were used from the trial to arrive at the populations listed above. There were six trials where HER2 status was unknown in at least one-third of the trial population, and one trial (Trial 0021) where approximately 20% of patients were not HR-positive. Not all trials focused on a post-menopausal population, but the authors attempted to obtain subgroup data for post-menopausal patients when available. However, it is not entirely clear that post-menopausal subgroup data were always obtained; for example, in their summary table of included trials (Table 7.2) the authors noted that although the HR was for the post-menopausal subgroup, the median PFS data were for the entire population in the MONARCH-2 trial.

The authors noted some differences in the patient populations enrolled in the trials that combined a CDK 4/6 inhibitor with fulvestrant (MONALEESA-3, MONARCH-2, PALOMA-3), which are summarized in Table 7.3. MONARCH-2 and PALOMA-3 included pre- and post-menopausal women, as well as those receiving both first- and second-line therapy. Approximately 80% of women were post-menopausal in both trials. According to the ITC authors, PALOMA-3 was the major outlier trial; and even when comparing similar subgroup data from this trial, the PFS results were clearly different between PALOMA-3 and MONALEESA-3 (Table 7.4). The authors therefore concluded that comparisons of ribociclib plus fulvestrant versus palbociclib plus fulvestrant based on the MONALEESA-3 and PALOMA-3 trials would not be feasible to reliably estimate relative efficacy between these two regimens. However, in contrast, they also concluded that because subgroup results from MONALEESA-3 and MONARCH-2 suggested similar efficacy between ribociclib plus fulvestrant and abemaciclib plus fulvestrant, it could be assumed that all CDK 4/6 inhibitors (including palbociclib plus fulvestrant) have similar efficacy across any populations in which they might be studied.

Table 7.2. Summary of trials included in the ITC

Trial/Source	Treatment	Control	Subgroups	Treatment Group Median PFS (months)	Control Group Median PFS (months)	HR [95% CI]	Notes
BOLERO-2	Ever + Exe	Exe	B	7.8	3.2	0.45 [0.38, 0.54]	Based on median PFS/HR for full population
BOLERO-2	Ever + exe	Exe	Bii + Biii	7.8	3.3	0.53 [0.41, 0.70]	
CONFIRM	Ful 500	Ful 250	Full, A	6.5	5.5	0.80 [0.68, 0.94]	HER2 status of patients unknown
EFECT	Ful 500/250mg	Exe	Full, A, Bii+Biii	3.7	3.7	0.96 [0.82, 1.13]	≥90% of patients were 2nd line
FALCON	Ful 500	AI	A	16.6	13.8	0.80 [0.64, 1.00]	<1% ER- and HER2+
MONALEESA-2	Rib + AI	AI	A	25.3	16	0.57 [0.46, 0.70]	
MONALEESA-3	Rib + ful 500	Ful 500	Full	20.5	12.8	0.59 [0.48, 0.73]	
MONALEESA-3	Rib + ful 500	Ful 500	A	NE	18.3	0.58 [0.42, 0.80]	
MONALEESA-3	Rib + ful 500	Ful 500	B	14.5	8.9	0.57 [0.35, 0.91]	
MONALEESA-3	Rib + ful 500	Ful 500	Bii + Biii	18.8	11.4	0.54 [0.33, 0.87]	
MONARCH-2	Abe + ful 500	Ful 500	Full, A, Bii + Biii	16.4	9.3	0.58 [0.46, 0.73]	HR is for post-menopausal subgroup; median PFS is for full population
MONARCH-3	Abe + AI	AI	A	NE	14.7	0.54 [0.41, 0.72]	
North American	Tam	AI	A	5.6	11.1	1.44 [1.16, 1.72]	HER2 status unknown in 39% of patients
PALOMA-2	Pal + AI	AI	A	24.8	14.5	0.58 [0.46, 0.72]	
PALOMA-3	Pal + ful 500	Ful 500	Full, A, Bii+Biii	9.9	3.9	0.45 [0.34, 0.59]	HR is for post-menopausal subgroup
PO25	AI	Tam	A	9.4	6.0	0.70 [0.60, 0.82]	HER2 status unknown in 33% of patients
SoFEA	Ful 250	Exe	Full, A, Bii+Biii	4.8	3.4	0.95 [0.79, 1.14]	HER2 status unknown in 33% of patients
TAMRAD	Ever + exe	Tam	Bii+Biii	8.6	4.5	0.54 [0.36, 0.81]	95% HER2-
TARGET	Tam	AI	A	8.3	8.2	0.99 [0.86, 1.12	HER2 status unknown in 39% of patients;
Trial 0021	Ful 500	AI	Bii + Biii	5.4	3.4	0.92 [0.74, 1.14]	HER2 status unknown; 80% ER+ +/- PR+

Abbreviations: Abe=abemaciclib; AI=aromatase inhibitor; CI=confidence interval; ER- = estrogen receptor negative; Ever=everolimus; Exe=exemestane; Ful=fulvestrant; HER2 = human epidermal growth factor receptor 2; HR=hazard ratio; NE=not estimable; Pal=palbociclib; PFS=progression-free survival; Tam=tamoxifen.

Summary of subgroups:
Full=full population in trial
A=1st line, excluding patients with disease free interval <12 months after (neo)adjuvant therapy
B=1st line refractory and 2nd line
Bii+Biii=2nd line

Source: Data from Table 5 in ITC report [58]

Table 7.3. Inclusion criteria for patient populations in trials of CDK4/6 inhibitors included in the ITC

Trial	CDK 4/6 inhibitor	Backbone ET	Relapse ≤12 months after adjuvant treatment with no prior ET for ABC	Relapse >12 months after adjuvant treatment with no Prior ET for ABC	De Novo ABC with no prior ET	Prior lines of ET in ABC	Menopausal Status
MONALEESA-3	Ribociclib	Fulvestrant	✓	✓	✓	1	Post
PALOMA-3	Palbociclib	Fulvestrant	✓	×	×	≥1	Any
MONARCH-2	Abemaciclib	Fulvestrant	✓	×	×	1	Any
MONALEESA-2	Ribociclib	AI	✓	✓	✓	0	Post
PALOMA-2	Palbociclib	AI	✓	✓	✓	0	Post
MONARCH-3	Abemaciclib	AI	×	✓	✓	0	Post
MONALEESA-7	Ribociclib	AI or Tamoxifen	✓	✓	✓	0	Pre/Peri

Abbreviations: ABC=advanced breast cancer; AI=aromatase inhibitor; CDK=cyclin dependent kinase; ET=endocrine therapy.

Source: Data from Table 6 in ITC report [58]

Table 7.4. Hazard ratios for PFS for subgroups from trials of CDK4/6 inhibitors used in combination with fulvestrant

Trial	Treatment	Comparator	Subgroup	Menopause Status		First-Line ET for ABC			Second-line ET in ABC	Third- or subsequent line ET in ABC	HR (95% CI)
							Prior (Neo)Adjuvant ET				
				Pre/ Peri	Post	De Novo	Relapse >12 Mo	Relapse ≤12 Mo			
MONALEESA-3	Rib+Ful	Ful	A		✓	✓	✓				0.55 (0.42, 0.72)
MONALEESA-3	Rib+Ful	Ful	B		✓			✓	✓		0.57 (0.44, 0.74)
MONALEESA-3	Rib+Ful	Ful	Bii&Biii		✓				✓		0.51 (0.33, 0.78)
PALOMA-3	Pal+Ful	Ful	ITT	✓	✓			✓	✓	✓	0.46 (0.36, 0.59)
PALOMA-3	Pal+Ful	Ful	Pre-/Peri-menopausal subgroup	✓				✓	✓	✓	0.50 (0.29, 0.87)
PALOMA-3	Pal+Ful	Ful	Post-menopausal subgroup		✓			✓	✓	✓	0.45 (0.34, 0.59)
PALOMA-3	Pal +Ful	Ful	Last therapy in adjuvant setting	✓	✓			✓			0.55 (0.32, 0.92)
PALOMA-3	Pal+Ful	Ful	Last therapy in metastatic setting	✓	✓				✓	✓	0.43 (0.32, 0.57)
MONARCH-2	Abe+Ful	Ful	ITT	✓	✓			✓	✓		0.55 (0.45, 0.68)
MONARCH-2	Abe +Ful	Ful	Pre/Peri-menopausal	✓				✓	✓		0.42 (0.25, 0.70)
MONARCH-2	Abe+Ful	Ful	Post-menopausal subgroup		✓			✓	✓		0.58 (0.46, 0.73)
MONALEESA-7	Rib+NSAI	NSAI	ITT	✓		✓	✓	✓			0.58 (0.48, 0.70)
MONALEESA-2	Rib +Let	Let	ITT		✓	✓	✓	✓			0.57 (0.46, 0.70)
PALOMA-2	Pal +Let	Let	ITT		✓	✓	✓	✓			0.58 (0.46, 0.72)
MONARCH-3	Abe +Let	Let	ITT		✓	✓	✓				0.54 (0.41, 0.72)

Abbreviations: ABC – advanced or metastatic breast cancer; Abe=abemaciclib; Ful=fulvestrant; HR=hazard ratio; ITT=intention-to-treat population; Let=letrozole; NSAI=non-steroidal aromatase inhibitor; Pal=palbociclib; Rib=ribociclib.

Source: Data from Table 7 in ITC report [58]

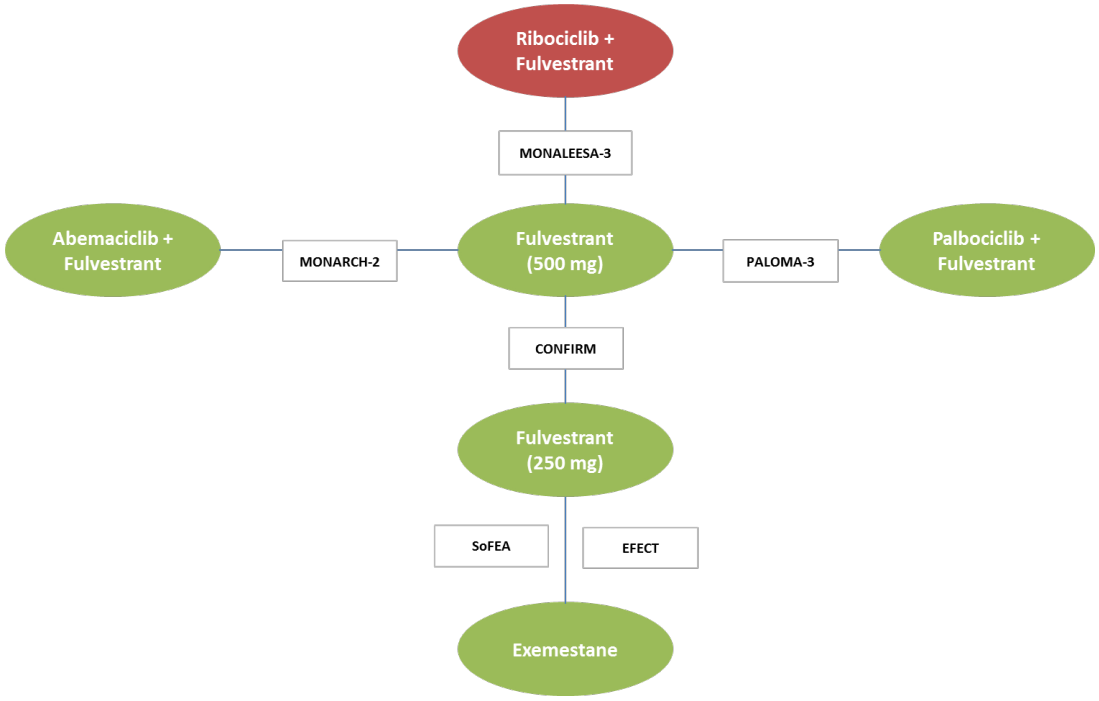
ITC Results

The reporting of the ITC results focuses on the comparisons between CDK 4/6 inhibitors.

Full (ITT) Population

For the ITC of the full population of MONALEESA-3, the analysis focused on trials that included post-menopausal women with HR-positive, HER2-negative ABC who had not received any prior treatment for ABC. However, it was noted that trials that included a mix of pre-/peri- and post-menopausal women with HER2-positive ABC were included where necessary (MONARCH-2 and PALOMA-3). Six trials were included in this evidence network (Table 7.5). The majority of the six pair-wise comparisons were informed by single trial connections and subgroups from trials (see Figure 7.1); subgroups of post-menopausal patients were extracted from MONARCH-2 and PALOMA-3.

Figure 7.1. Evidence network for full population



Source: ITC Report [58]

Table 7.5. Hazard ratios for PFS used in the ITC from trials of patients with HR-positive, HER2-negative ABC for the Full Population of MONALEESA-3

Trial	Study Arm		HR (95%CI)	Comment
	Treatment	Control		
MONALEESA-3	Rib + Ful 500	Ful 500	0.59 (0.49, 0.71)	All patients
CONFIRM	Ful 500	Ful 250	0.80 (0.68, 0.94)	
SoFEA	Ful 500/250	Exe	0.95 (0.79, 1.14)	Patients in fulvestrant arm received 500 mg intramuscularly on day 0, 250 mg on days 14, 28, and 250 mg every 28 days thereafter. In the ITC, this was assumed to be equivalent in efficacy to fulvestrant 250 mg.
EFECT	Ful 500/250	Exe	0.96 (0.82, 1.13)	Patients in fulvestrant arm received 500 mg intramuscularly on day 0, 250 mg on days 14, 28, and 250 mg every 28 days thereafter. In the ITC, this was assumed to be equivalent in efficacy to fulvestrant 250 mg.
MONARCH-2	Abe + Ful 500	Ful 500	0.58 (0.46, 0.73)	Based on the subgroup for post-menopausal patients
PALOMA-3	Pal + Ful 500	Ful 500	0.45 (0.34, 0.59)	Based on the subgroup for post-menopausal patients; includes patients with 2 or more prior lines of ET

Abbreviations: Abe=abemaciclib; CI=confidence interval; ET=Endocrine therapy; Exe=exemestane; Ful=fulvestrant; HR=hazard ratio; ITT=intention to treat population; Let=letrozole; NSAI=non-steroidal aromatase inhibitor; Pal=palbociclib. Rib=ribociclib

Source: Data from Table 8 in ITC report [58]

The ITC results for the Full Population (Table 7.6) show that all three CDK 4/6 inhibitors when combined with fulvestrant achieved a statistically significant improvement in PFS versus fulvestrant alone, based on CIs that do not include the null hypothesis value (i.e., HR=1.00). Ribociclib plus fulvestrant was also shown to be superior to exemestane monotherapy. There was no clear difference in efficacy between ribociclib plus fulvestrant and palbociclib plus fulvestrant or abemaciclib plus fulvestrant.

Table 7.6. HRs for PFS from ITC of Trials of Patients with HR+/HER2- ABC for the Full Population of MONALEESA-3

Comparator	HR (95%CI) of Comparator vs.	
	Fulvestrant	Ribociclib plus Fulvestrant
Fulvestrant 500 mg	1.00 (n/a, n/a)	1.70 (1.42, 2.05)
Ribociclib + Fulvestrant 500 mg	0.59 (0.49, 0.71)	1.00 (n/a, n/a)
Palbociclib + Fulvestrant 500 mg	0.45 (0.34, 0.59)	0.77 (0.55, 1.07)
Abemaciclib + Fulvestrant 500 mg	0.58 (0.46, 0.73)	0.99 (0.74, 1.33)
Exemestane	1.31 (1.07, 1.60)	2.22 (1.69, 2.92)

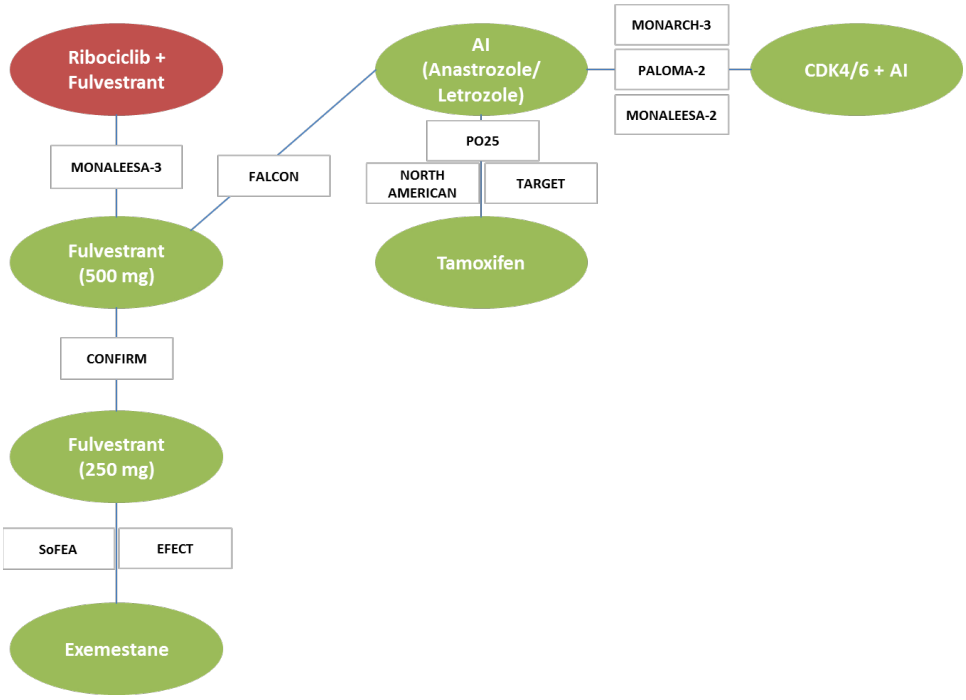
Abbreviations: CI=confidence interval; HR=hazard ratio; n/a=not applicable

Source: Data from Table 9 in ITC report [58]

Group A (ET sensitive: First-line, excluding patients with disease-free interval <12 months after [neo]adjuvant therapy)

For the analysis referred to as 'Group A', only the trials of post-menopausal, HR-positive women who had not received prior therapy were included. There were 11 trials included in this network (see Table 7.7) and six pairwise comparisons (see Figure 7.2). Group A compared ribociclib plus fulvestrant to other CDK 4/6 inhibitors combined with an AI (PALOMA-2, MONARCH-3) (Table 7.7). These were the trials involving CDK 4/6 inhibitors that were in a de novo ABC population (refer to Table 7.3).

Figure 7.2. Evidence network for Group A



Source: ITC report[58]

Table 7.7. Hazard ratios for PFS used in the ITC of trials of patients with HR-positive, HER2-negative ABC in Group A

Trial	Study Arm		HR (95%CI)	Comment
	Treatment	Control		
MONALEESA-3	Rib + Ful 500	Ful 500	0.55 (0.42, 0.72)	Group A patients
PALOMA-2	Pal + AI	AI	0.58 (0.46, 0.72)	Post-menopausal patients
MONARCH-3	Abe + AI	AI	0.54 (0.41, 0.72)	Post-menopausal patients
MONALEESA-2	Rib + AI	AI	0.57 (0.46, 0.70)	
CONFIRM	Ful 500	Ful 250	0.80 (0.68, 0.94)	HER2 status was not evaluated
SoFEA	Ful 250	Exe	0.95 (0.79, 1.14)	Includes 2L+ patients, 7% were HER2+
EFECT	Ful 250	Exe	0.96 (0.82, 1.13)	Includes 2L+ patients
FALCON	Ful 500	AI	0.80 (0.64, 1.00)	
PO25	AI	Tamoxifen	0.70 (0.60, 0.82)	
North American	Tamoxifen	AI	1.44 (1.16, 1.72)	
TARGET	Tamoxifen	AI	0.99 (0.86, 1.12)	

Abbreviations: 2L=2nd line; Abe=abemaciclib; AI=aromatase inhibitor; CI=confidence interval; Exe=exemestane; Ful=fulvestrant; HER2+ = human epidermal growth factor receptor positive; HR=hazard ratio; Pal=palbociclib; Rib=ribociclib

Source: Data from Table 10 in ITC report [58]

The ITC results for Group A (Table 7.8) showed no evidence of a difference in efficacy between ribociclib plus fulvestrant and the other CDK 4/6 inhibitors plus an AI, either palbociclib (HR of 1.33 [95% CI: 0.88, 2.03] or abemaciclib (HR of 1.24 [95% CI: 0.79, 1.95]). Comparing ribociclib plus fulvestrant to pooled results from all CDK 4/6 inhibitors plus AI, produced an HR of 1.30 (95% CI: 0.96, 1.81).

Table 7.8. Hazard ratios for PFS from the ITC of trials of patients with HR-positive, HER2-negative ABC in Group A

Comparator	HR (95%CI) of Comparator vs.	
	Fulvestrant	Ribociclib plus Fulvestrant
Fulvestrant 500 mg	1.00 (n/a, n/a)	1.83 (1.39, 2.41)
Ribociclib + Fulvestrant 500 mg	0.55 (0.42, 0.72)	1.00 (n/a, n/a)
CDK4/6 + AI (pooled)	0.71 (0.59, 0.89)	1.30 (0.96, 1.81)
Ribociclib + AI	0.71 (0.52, 0.97)	1.31 (0.86, 1.98)
Palbociclib + AI	0.73 (0.53, 1.00)	1.33 (0.88, 2.03)
Abemaciclib + AI	0.68 (0.47, 0.97)	1.24 (0.79, 1.95)
Aromatase Inhibitor	1.25 (1.00, 1.57)	2.30 (1.61, 3.28)
Exemestane	1.31 (1.07, 1.60)	2.39 (1.70, 3.36)

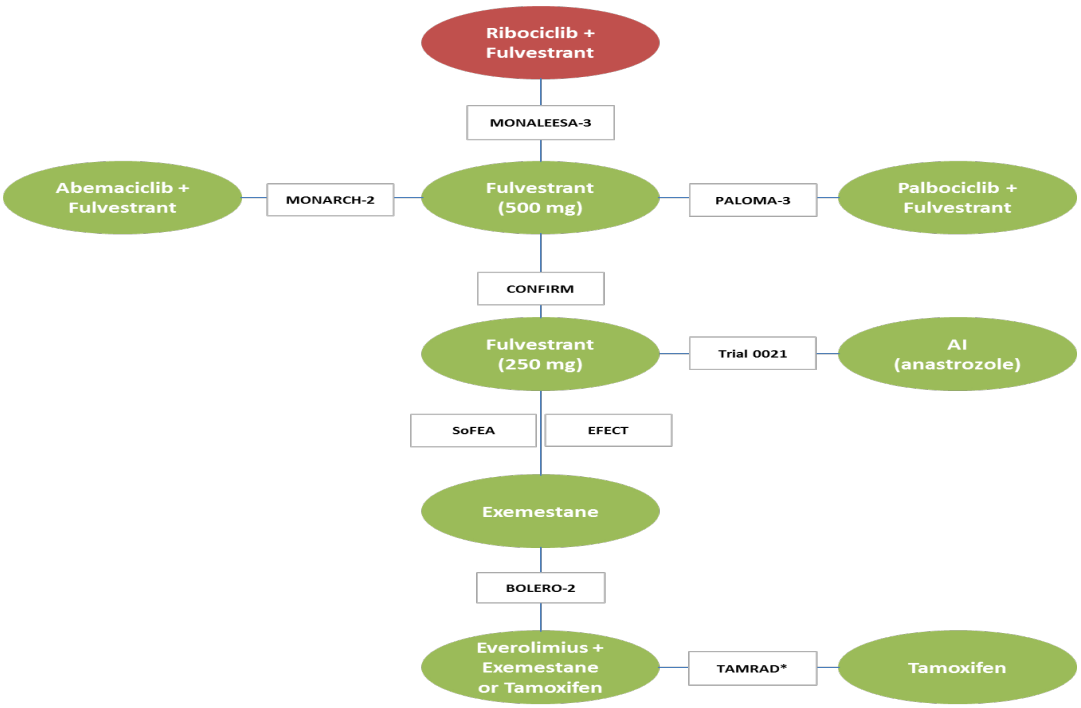
Abbreviations: AI=aromatase inhibitor; CDK=cyclin dependent kinase; CI=confidence interval; HR=hazard ratio.

Source: Data from Table 11 in ITC report [58]

Group Bii and Biii (Second-line)

For the Group Bii and Biii analysis, the authors used the same subgroup data for palbociclib plus fulvestrant and abemaciclib plus fulvestrant as they had for the full population and the Group B analysis. There were nine trials in this network (Table 7.9) involving eight pairwise comparisons that were primarily informed by single trials (Figure 7.3).

Figure 7.3. Evidence network for Groups Bii and Biii



Source: ITC report[58]

Table 7.9. Hazard ratios used in the ITC of PFS in patients with HR-positive, HER2-negative ABC in Groups Bii and Biii

Trials	Intervention	Control	HR [95% CI]	Comment
MONALEESA-3	Rib + ful 500	Ful 500	0.51 (0.33, 0.78)	Bii and Biii
Trial 0021	Ful 250	AI	0.92 (0.74, 1.14)	
CONFIRM	Ful 500	Ful 250	0.80 (0.68, 0.9)]	
SoFEA	Ful 250	Exe	0.95 (0.79, 1.14)	Includes 1L patients
EFECT	Ful 250	Exe	0.96 (0.82, 1.13)	Includes 1L patients
BOLERO-2	Ever + exe	Exe	0.53 (0.41, 0.70)	Includes 2L patients
TAMRAD	Ever + exe	Tam	0.54 (0.36, 0.81)	
MONARCH-2	Abe + Ful 500	Ful 500	0.58 (0.46, 0.73)	Based on the subgroup for post-menopausal patients
PALOMA-3	Pal + Ful 500	Ful 500	0.45 (0.34, 0.59)	Based on the subgroup for post-menopausal patients; includes patients with 2 or more prior lines of ET

Abbreviations:1L=first line; 2L=second line; Abe=abemaciclib; AI=aromatase inhibitor; CI=confidence interval; Ever=everolimus; Exe=exemestane; ET=endocrine therapy; Ful=fulvestrant; HR=hazard ratio; Pal=palbociclib; Rib=ribociclib

Source: Data from Table 12 in ITC report [58]

The ITC results for Groups Bii and Biii showed no evidence of a clear and consistent difference in efficacy with respect to PFS between ribociclib plus fulvestrant and the other CDK 4/6 inhibitors plus fulvestrant, palbociclib (HR of 0.89 [95% CI: 0.53, 1.49]) or abemaciclib (1.15 [95% CI: 0.70, 1.88]). Ribociclib plus fulvestrant was more efficacious than AI (HR of 2.69 [95% CI: 1.62, 4.48]), exemestane (HR of 2.59 [95% CI: 1.61, 4.17]), and tamoxifen (HR of 2.55 [95% CI: 1.29, 5.06]). There did not appear to be a difference between ribociclib plus fulvestrant and the combination of everolimus plus exemestane (HR of 1.38 [95% CI: 0.80, 2.39]).

There were a few assumptions made within this network that should be noted. There were no trials of tamoxifen as second-line treatment identified, and therefore tamoxifen was connected to the evidence network through the TAMRAD trial, which compared everolimus plus tamoxifen with tamoxifen alone. It was assumed that everolimus plus tamoxifen are equivalent to everolimus plus exemestane with respect to effects on PFS. Additionally, the BOLERO-2 trial did not appear to report the HR for PFS by line of treatment for everolimus plus exemestane versus exemestane alone, and therefore the authors had to use patient level data to identify patients who had received only one prior line of therapy in the metastatic setting. The HR was then estimated using a Cox proportional hazard model.

Table 7.10. Hazard ratios for PFS from the ITC of trials of patients with HR-positive, HER2-negative ABC in Groups Bii and Biii

Comparator	HR (95%CI) of Comparator vs.	
	Fulvestrant	Ribociclib plus Fulvestrant
Fulvestrant 500 mg	1.00 (n/a, n/a)	1.98 (1.29, 3.05)
Ribociclib + Fulvestrant 500 mg	0.50 (0.33, 0.78)	1.00 (n/a, n/a)
Palbociclib + Fulvestrant 500 mg	0.45 (0.34, 0.59)	0.89 (0.53, 1.49)
Abemaciclib + Fulvestrant 500 mg	0.58 (0.46, 0.73)	1.15 (0.70, 1.88)
Aromatase Inhibitor	1.36 (1.04, 1.78)	2.69 (1.62, 4.48)
Exemestane	1.31 (1.07, 1.60)	2.59 (1.61, 4.17)
Everolimus + Exemestane	0.70 (0.49, 0.98)	1.38 (0.80, 2.39)
Tamoxifen	1.29 (0.76, 2.19)	2.55 (1.29, 5.06)

Abbreviations: CI=confidence interval; HR=hazard ratio; n/a=not applicable.

Source: Data from Table 13 in ITC report [58]

Group B (ET resistant: Second-line and First-line Refractory)

The ITC for Group B used the same evidence network as Groups Bii and Biii; refer to Table 7.11 for the list of included trials.

Table 7.11. Hazard ratios of PFS used in the ITC of trials in patients with HR-positive, HER2-ABC in Group B

Trial	Study Arm		HR (95%CI)	Comment
	Experimental	Control		
MONALEESA-3	Rib + Ful 500	Ful 500	0.57 (0.44, 0.74)	Group B patients
Trial 0021	Ful 250	AI	0.92 (0.74, 1.14)	
CONFIRM	Ful 500	Ful 250	0.80 (0.68, 0.94)	HER2 status was not evaluated
SoFEA	Ful 250	Exe	0.95 (0.79, 1.14)	Includes 1L patients, 7% of patients were HER2+
EFECT	Ful 250	Exe	0.96 (0.82, 1.13)	Includes 1L patients
BOLERO-2	Ever + Exe	Exe	0.45 (0.38, 0.54)	Includes 1L patients
TAMRAD	Ever + Exe	Tamoxifen	0.54 (0.36, 0.81)	
MONARCH-2	Abe + Ful 500	Ful 500	0.58 (0.46, 0.73)	Based on the subgroup for postmenopausal patients
PALOMA-3	Pal + Ful 500	Ful 500	0.45 (0.34, 0.59)	Based on the subgroup for postmenopausal patients; includes patients with 2 or more prior lines of ET

Abbreviations: 1L=first line; 2L=second line; Abe=abemaciclib; AI=aromatase inhibitor; ET=endocrine therapy; Ever=everolimus; Exe=exemestane; Ful=fulvestrant; HER2=Human epidermal growth factor receptor 2; Pal=palbociclib; Rib=ribociclib.

Source: Data from Table 14 in ITC report [58]

The ITC results for Group B (Table 7.12) suggest that the combination of ribociclib and fulvestrant improves PFS when compared to AI (HR of 2.38 [95% CI: 1.64, 3.45]), fulvestrant alone (HR of 1.75 [95% CI: 1.36, 2.26]), exemestane (HR of 2.29 [95% CI: 1.65, 3.17]) and tamoxifen (HR of 1.91 [95% CI: 1.10, 3.30]). There was no evidence of a clear difference in PFS between ribociclib plus fulvestrant and other CDK 4/6 inhibitors plus fulvestrant, either palbociclib (HR of 0.79 [95% CI: 0.54, 1.15]) or abemaciclib (HR of 1.02 [95% CI: 0.72, 1.43]).

Table 7.12. Hazard ratios for PFS from the ITC of trials of patients with HR-positive, HER2-negative ABC in Group B

Comparator	HR (95%CI) of Comparator vs.	
	Fulvestrant	Ribociclib plus Fulvestrant
Fulvestrant 500 mg	1.00 (n/a, n/a)	1.75 (1.36, 2.26)
Ribociclib + Fulvestrant 500 mg	0.57 (0.44, 0.74)	1.00 (n/a, n/a)
Palbociclib + Fulvestrant 500 mg	0.45 (0.34, 0.59)	0.79 (0.54, 1.15)
Abemaciclib + Fulvestrant 500 mg	0.58 (0.46, 0.73)	1.02 (0.72, 1.43)
Aromatase Inhibitor	1.36 (1.04, 1.78)	2.38 (1.64, 3.45)
Exemestane	1.31 (1.07, 1.60)	2.29 (1.65, 3.17)
Everolimus + Exemestane	0.59 (0.45, 0.77)	1.03 (0.71, 1.49)
Tamoxifen	1.09 (0.67, 1.77)	1.91 (1.10, 3.30)
Abbreviations: CI=confidence interval; HR=hazard ratio; n/a = not applicable. Source: Data from Table 15 in ITC report [58]		

Adverse Events

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

Table 7.13: Adverse Events (Grade 3+)

Adverse Events	Rib + ful	Pal + ful	Abe + ful	Ful	Ever + exe	Exe	Tam	Rib + AI	Pal + AI	Abe + AI	Let
Abnormal LFTs	0%	0%	0%	0%	0%	0%	0%	10%	0%	0%	2%
Anemia	3%	3%	7%	2%	8%	0%	0%	2%	5%	6%	1%
Decreased leukocyte count	14%	26%	9%	0%	0%	0%	0%	21%	25%	8%	1%
Diarrhea	1%	0%	13%	0%	3%	0%	0%	2%	1%	10%	1%
Fatigue	2%	3%	3%	1%	5%	1%	11%	3%	2%	2%	1%
Hypertension	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Increased ALT	0%	0%	4%	2%	4%	2%	0%	0%	0%	6%	2%
Increased GGT	0%	0%	0%	0%	7%	7%	0%	0%	0%	0%	0%
Infection	0%	2%	0%	3%	0%	0%	5%	0%	0%	5%	3%
Neutropenia	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	1%
Neutropenia asymptomatic	53%	62%	27%	0%	0%	0%	0%	62%	67%	21%	0%
Pain	0%	0%	0%	0%	0%	0%	18%	0%	0%	0%	0%
Pneumonia	0%	0%	0%	0%	7%	0%	0%	0%	0%	0%	0%
PNNs	0%	0%	0%	0%	0%	0%	5%	0%	0%	0%	0%
PPE syndrome	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%
Stomatitis	0%	0%	1%	0%	8%	0%	0%	0%	0%	0%	0%

Abbreviations: Abe=abemaciclib; AI=aromatase inhibitor; ALT=alanine aminotransferase; CT=chemotherapy; Exe=exemestane; Ever=everolimus; Ful=fulvestrant; GGT=gamma glutamyl transferase; Let=letrozole; LFT=liver function tests; Pal=palbociclib; PPE=palmar plantar erythrodysesthesia; Rib=ribociclib; Tam=tamoxifen.

Source: Data from Tables 16 and 17 in ITC report [58]

Conclusions of ITC

The authors noted the limitations of the ITCs, most notably the significant heterogeneity between included trials, and in this context concluded that ribociclib plus fulvestrant is an effective treatment option for patients with HR-positive, HER2-negative ABC.

Critical Appraisal

The quality of the submitted ITC was assessed according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons Questionnaire. Details of the critical appraisal are presented in Table 7.14.

Several ITCs were presented based on different populations in the MONALEESA-3 trial: full population, first-line (ET sensitive) patients and second-line patients (endocrine resistant patients). MONALEESA-3 was the only trial that focused exclusively on a post-menopausal population in patients being treated with a CDK 4/6 inhibitor combined with fulvestrant. In order to compare ribociclib to other CDK 4/6 inhibitors on a background of fulvestrant, the authors had to use subgroup data from PALOMA-3 and MONARCH-2, both trials that enrolled a mixed population of pre-/peri- and post-menopausal patients. The authors also emphasized that PALOMA-3 was an outlier with respect to results (compared to the trials ribociclib and abemaciclib) and suggested that comparing ribociclib plus fulvestrant to palbociclib plus fulvestrant was therefore not feasible to reliably estimate relative efficacy between these two drug combinations. While MONALEESA-3 included patients with do novo breast cancer who had

not received prior ET, and patients who had early breast cancer at diagnosis with relapse >12 months after completing (neo)adjuvant ET and with no prior ET for ABC, PALOMA-3 did not include these patients. In addition, PALOMA-3 included patients who had received two or more prior lines of ET for ABC while MONALEESA-3 did not include these patients. The authors also cited the PFS results from PALOMA-3 compared to MONALEESA-3 as evidence of how different the patient populations were. The authors assumed that because findings between ribociclib plus fulvestrant and abemaciclib and fulvestrant were similar, that all CDK 4/6 inhibitors could be considered to have similar efficacy. The authors did not attempt to perform any meta-regression in order to try to account for this heterogeneity, therefore the comparisons between CDK 4/6 inhibitors on a background of fulvestrant should be interpreted with caution, as any differences (or lack of differences) reported may have been influenced by differences in study populations. There were no trials of palbociclib or abemaciclib plus fulvestrant for first-line use, therefore no conclusions could be drawn about this patient population.

The authors also added CDK 4/6 inhibitors plus AI/NSAI as comparators at the request of pCODR; however, any comparisons between ribociclib plus fulvestrant and other CDK 4/6 inhibitors plus AI/NSAI are clearly limited by the use of different background therapies.

Overall, the significant heterogeneity between the trials included in the ITCs is a major limitation, and therefore the results of the analyses should be interpreted with caution. The baseline characteristics of patient populations in the included trials were not adequately described, however, as noted above, there were 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 (patient demographics, study locations, PFS definitions and assessment schedule, median follow-up time) was not reported. Due to 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; 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 and objective response were not included in the analysis. Patient-reported outcomes were also not included in the ITC. 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 treatments; however, the naïve comparison performed suggests the CDK inhibitors, as a group, appear to carry a higher risk of various cytopenias, mainly neutropenia, when compared to other therapies.

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

Table 7.14. 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. Post-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 a 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.
3. Are any relevant outcomes missing?	**Yes. The ITC focused on PFS, which is a priority efficacy outcome. However, other outcomes including OS, ORR, time-to-response, DOR 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 randomized controlled trials?	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 network of randomized controlled trials?	Yes.
7. Is it apparent that poor quality studies were included thereby leading to bias?	Unclear. Details regarding study design were not provided, though RCTs were sought. **The results of the quality assessment of individual trials were not reported.**
8. Is it likely that bias was induced 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.**

ISPOR Questions	Details and Comments‡
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 analyses actually performed.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Unknown.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Yes, in part.** Subgroup analyses were performed although they were limited by the available data.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	A figure illustrating the evidence network was provided, and this identifies the specific trials contributing to each comparison in the evidence networks.
19. Are the individual study results reported?	Yes. Treatment effect estimates for PFS were reported for individual 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 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.

7.1.1 Summary

As the MONALEESA-3 trial did not include a comparison to an active relevant comparator, the sponsor conducted an ITC to estimate the relative efficacy (PFS) and safety of ribociclib plus fulvestrant versus other treatments for patients with HR-positive, HER2-negative ABC. The ITC was conducted in order to provide inputs into the pharmacoeconomic model supporting the reimbursement request. Eligible trials were identified from a systematic review of electronic databases performed in April 2018 seeking RCTs and was supplemented with trials identified through a more targeted review of the literature. The ITC of PFS was conducted using the Bucher method, while adverse events were evaluated using an unanchored (naïve) comparison. The sponsor conducted several ITCs, each with a different patient population derived from the MONALEESA-3 trial: the full trial population, ET sensitive patients receiving first-line therapy (which excluded patients with a disease-free interval <12 months after (neo)adjuvant therapy), ET resistant patients who were either first-line ET refractory or were receiving second-line therapy, or patients receiving second-line therapy only.

A total of 16 trials were included in the ITC, which evaluated treatments including CDK 4/6 inhibitor-based therapies (palbociclib or abemaciclib), AI, fulvestrant, tamoxifen, and everolimus with or without exemestane. Treatment comparisons were dependent on what trials could be connected in each ITC evidence network. Not all trials focused on a post-menopausal population, however the authors tried to obtain subgroup data for post-menopausal patients when available. For the full population, the ITC results showed that all three CDK 4/6 inhibitors when combined with fulvestrant achieved a statistically significant improvement in PFS versus fulvestrant alone. Ribociclib plus fulvestrant was also shown to be superior to exemestane monotherapy, and there was no clear difference in efficacy between ribociclib plus fulvestrant and palbociclib plus fulvestrant or abemaciclib plus fulvestrant. There were no trials of palbociclib or abemaciclib plus fulvestrant in the first-line (ET sensitive), thus comparisons for this patient subgroup were between ribociclib plus fulvestrant and CDK 4/6 inhibitors combined with an AI; results from these comparisons showed no evidence of a difference in efficacy between ribociclib plus fulvestrant and the other CDK 4/6 inhibitors plus an AI. The ITC results for the second-line (ET resistant) and ET refractory subgroups were similar, as these subgroups used the same evidence network; results showed no differences in efficacy between ribociclib plus fulvestrant and the other CDK 4/6 inhibitors plus fulvestrant or everolimus plus exemestane. No conclusions could be drawn about the relative harms of the CDK 4/6 inhibitors, as only a naïve comparison was presented; however, various cytopenias, most notably neutropenia, appear to be an adverse effect associated with the CDK 4/6 inhibitors.

The pCODR Methods Team considered the significant heterogeneity in patient populations among the included trials as a major limitation of the ITC; there were notable differences across the trials related to menopausal status, endocrine partner, disease-free interval, inclusion of de novo ABC patients, and line of therapy, as well as missing information on other important patient and trial characteristics. Overall, the ITC results should be interpreted with caution given the significant clinical heterogeneity across trials that could impact their comparability to the MONALEESA-3 trial and produce biased estimates of relative treatment effect.

8 COMPARISON WITH OTHER LITERATURE

No relevant 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 plus fulvestrant for 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 no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

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).[59]

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).[60]

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. 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 Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

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

Writing of the Review Report

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

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

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