CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Abemaciclib (Verzenio) for Metastatic Breast Cancer

July 5, 2019

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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 abemaciclib for advanced or metastatic breast cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

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

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

1.1 Introduction

The reimbursement request is for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer:

- In combination with an aromatase inhibitor in postmenopausal women as initial endocrine based therapy. (Endocrine Naïve/Sensitive, also referred to as First-Line Systemic Therapy/Endocrine Sensitive)
- In combination with fulvestrant in women with disease progression following endocrine therapy. Pre- or perimenopausal women must also be treated with a gonadotropin-releasing hormone agonist. (Endocrine-Resistant)

The Health Canada approved indication aligns with the reimbursement request. Of note, according to the Health Canada Product Monograph, the clinical effectiveness of VERZENIO in combination with an aromatase inhibitor (AI) is based on the benefit observed in patients treated with abemaciclib in combination with letrozole or anastrozole for the treatment of postmenopausal women with advanced breast cancer. [1]

When used in combination with endocrine (aromatase inhibitor or fulvestrant) therapy, the recommended dose of abemaciclib is 150 mg taken orally, twice daily until disease progression or unacceptable toxicity.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two randomized controlled trials. The results of the MONARCH 3 (Endocrine-Naïve/Sensitive) (N=579) and MONARCH 2 (Endocrine-Resistant) (N=669) trials are as follows (Table 1.1):

MONARCH 3 (Endocrine-Naïve/Sensitive)

MONARCH 3 was a phase III, multi-centre, randomized, double-blind, placebo-controlled study of abemaciclib or placebo plus a nonsteroidal AI in postmenopausal women with HR+/HER2− advanced or metastatic breast cancer who had not received any previous systemic therapy in the advanced/metastatic setting. Eligible patients were randomized to receive abemaciclib + AI (anastrozole or letrozole per physician's choice) or placebo + AI.[2,3]

A total of 493 patients were included in the MONARCH 3 trial, with 328 patients in the abemaciclib + AI arm and 165 in the placebo + arm. The baseline demographic and disease characteristics were well balanced between the study arms. All enrolled patients were female and post-menopausal, with the median age of 63 years (range 32 to 88). The majority of patients were White (56.7%, and 61.8% in the abemaciclib and placebo arms, respectively) or Asian (31.4%, and 27.3% in the abemaciclib and placebo arms, respectively); and had a measurable disease (81.4%, and 78.8% in the abemaciclib and placebo arms, respectively). Prior treatments were also well-balanced between the two study arms. Approximately 40% of the patients in each arm had received a prior adjuvant or neoadjuvant chemotherapy. At the baseline, 25.9% of patients in the abemaciclib + AI arm and 30.3% of those in the placebo + AI arm had received a prior AI.[2]

Efficacy (Endocrine-Naïve/Sensitive)

The primary efficacy endpoint was investigator-assessed progression-free survival (PFS; according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1). Key secondary end points included objective response rate (ORR), duration of response, overall survival (OS) and clinical benefit rate (CBR).[2,3]

Progression-Free Survival (Endocrine-Naïve/Sensitive)

As of the 31-Jan-2017 data cut-off date, after a median follow-up duration of 17.8 months, a total of 108 patients (32.9%) in the abemaciclib + AI arm and 86 patients (52.1%) in the placebo + AI arm had a PFS event.[2,3] The median PFS was not reached in the abemaciclib + AI arm and was 14.7 months with placebo + AI (HR = 0.54; 95% CI 0.41 to 0.72; P = 0.000021). The results of the blinded central analysis were consistent with those of the primary analysis (HR = 0.51; 95% CI 0.36 to 0.72; P =0.000102). The PFS benefit was maintained across pre-defined patient subgroups. [2,3]

At the 07-Nov-2017 data cut-off, after a median follow-up duration of 26.73 months, 246 investigator-assessed PFS events had occurred (138 [42.1%] events the abemaciclib + AI arm and 108 [65.5%] events in the placebo + AI arm). The median PFS was 28.18 months in the abemaciclib + AI arm compared to 14.76 months in the placebo+ AI arm (HR = 0.540; 95% CI 0.418, 0.698); p = 0.000002). In the subgroup analysis, PFS benefit maintained across the pre-defined patient.[4]

Overall Survival (Endocrine-Naïve/Sensitive)

At the 31-Jan-2017 data cut-off date, OS results were immature, with a total of 49 deaths (32 deaths [9.8%] in the abemaciclib + AI arm and 17 deaths [10.3%] in the placebo + AI arm). The median OS was not reached in neither of the arms.[2,3] The final OS analysis is planned to be performed after occurrence of 315 death events.

Objective Response Rate (Endocrine-Naïve/Sensitive)

As of the 31-Jan-2017 data cut-off date, ORR was reported to be 48.2% (95% CI, 42.8% to 53.6%) in the abemaciclib + AI arm and 34.5% (95% CI, 27.3% to 41.8%) in the placebo + AI arm (P = 0.002).[2] For patients with measurable disease, ORR was 59.2% (95% CI 53.3%, 65.1%) in the abemaciclib + AI arm and 43.8% (95% CI 35.3%, 52.4%) in the placebo + AI arm (P = 0.004). The median duration of

response was not reached in the abemaciclib + AI arm and was 14.1 months in the placebo + AI arm.[2]

At the 07-Nov-2017 data cu-off date, the ORR was 49.7% (95% CI 44.3%, 55.1%) in the abemaciclib + AI arm and 37.0% (95% CI 29.6%, 44.3%) in the placebo + AI arm (p = 0.005). For the subset of 399 patients (80.9%) with measurable disease, the ORR was 61.0% (95% CI 55.2%, 66.9%) in the abemaciclib + AI arm and 45.5% (95% CI 37.0%, 53.9%) in the placebo arm (p = 0.003). The median duration of response was 27.39 months in the abemaciclib + AI arm and17.46 months in the placebo + AI arm.[4]

Clinical Benefit Rate (CBR) (Endocrine-Naïve/Sensitive)

At the time of data cut-off, CBR was achieved by 78.0% pf patients (95% CI 73.6%, 82.5%) in the abemaciclib + AI arm and 71.5% of patients (95% CI 64.6%, 78.4%) in the placebo arm.[2]

Quality of Life (Endocrine-Naïve/Sensitive)

No peer-reviewed publications reporting on the quality of life data from the MONARCH 3 trial were identified in this pCODR review. The following data has been extracted from a conference abstract and its related poster presentation that was provided by the Submitter:

A clinically meaningful (≥ 10 points) and statistically significant worsening in diarrhea was reported in the abemaciclib + AI arm. There was a statistically significant and clinically meaningful worsening in EORTC QlQ-C30 diarrhea symptom score in abemaciclib-treated patients (mean change = 18.68; 95% CI 15.13, 22.22; p<0.001). Changes from baseline in the following symptom scores were statistically different (but not clinically meaningful) between the two study arms, all favoring the placebo arm: nausea and vomiting (mean change = 2.77; 95% CI 0.58, 4.97; p = 0.013), appetite loss (mean change = 4.03; 95% CI 0.31, 7.74; p = 0.034), and fatigue (mean change = 4.96; 95% CI 1.58, 8.35; p=0.004). In addition, a statistically significant worsening was observed with abemaciclib in global health status, role functioning, social functioning, body image, and the composite score for the systemic therapy symptoms.[5] More details can be found in Section 6.

Harms (Endocrine-Naïve/Sensitive)

As of the 31-Jan-2017 data cut-off date, after a median follow-up of 17.8 months, 98.8% of patients in the abemaciclib + AI arm and 94.4% of those in the placebo + AI arm had at least one reported treatment emergent AE. In the abemaciclib + AI arm, the most common AEs (any grade reported by≥30% of the patients) included diarrhea, neutropenia, fatigue, nausea, anemia, abdominal pain, and vomiting.[6] Grade 3 and 4 treatment emergent AEs were reported in 61.8% of abemaciclib-treated patients and 26.1% of placebo-treated patients.[6] SAEs were reported in 31.2% of patients in the abemaciclib + AI arm and 16.8% of those in the placebo + AI arm. Withdrawal rate due to AEs in the abemaciclib + AI arm (16.5%) was higher than that in the placebo + AI arm (3.1%). Death due to an AE was reported for eight patients (2.4%) receiving abemaciclib + AI and one patient (0.4%) receiving placebo + AI.[6]

At the time of the 90-day safety update (11-Aug-2017), a total of 16 deaths were reported: 13 deaths with abemaciclib + AI and three with placebo + AI. The updated results included no new safety signals.[3]

As of 07-Nov-2017, a total of 323 patients (98.8%) in the abemaciclib + AI arm and 152 patients (94.4%) in the placebo + AI arm were reported with at least one AE. Diarrhea was the most common AE in the abemaciclib-treated patients (82.3% versus 32.3% in the placebo arm; discontinuation due to diarrhea for the abemaciclib + NSAI group was low (1.8% versus 0%). Neutropenia occurred in 43.7% of abemaciclib-treated patients compared with 1.9% in the placebo arm. Dose reductions due to AEs occurred for 46.5% of patients receiving abemaciclib + AI and 6.2% of those receiving placebo + AI. Overall, 25.1% of patients in the abemaciclib + AI arm and 4.3% of those in the placebo + AI arm discontinued any study drug due to an AE. A total of 18 deaths were reported: 15 deaths with abemaciclib + AI (11 due to AEs) and three deaths (1.9%) with placebo + AI (two due to AEs).[4]

MONARCH 2 (Endocrine-Resistant)

MONARCH 2 was a phase III, multi-centre, randomized, double-blind, placebo-controlled study of fulvestrant with or without abemaciclib in women with HR+/HER2− advanced or metastatic breast cancer whose disease had progressed on previous endocrine therapy.[7,8] Eligible patients were randomized in a 2:1 ratio to receive abemaciclib + fulvestrant or placebo + fulvestrant (28-day cycles). All pre- or peri-menopausal women were also treated with a gonadotropin-releasing hormone agonist.[9] The initial study design included patients with or without prior endocrine therapy in the advanced or metastatic setting. However, the study was amended (Amendment b)

to exclude endocrine-naïve patients. Therefore, the ITT population included endocrine therapy pre-treated (endocrine-resistant) patients, defined as patients who had disease progression ≤12 months of completing adjuvant endocrine therapy or those who had progressed on or after first-line endocrine therapy for metastatic disease.[9]

A total of 669 patients with endocrine-resistant disease were enrolled in the trial. Baseline demographic and disease characteristics of the study population were well balanced between the study arms. All enrolled patients were female, with the median age of 60 years (range 32 to 91). The majority of patients were White or Asian (33.4% and 29.1% in the abemaciclib and placebo arms, respectively); in a post-menopausal status (83.2%, and 80.7% in the abemaciclib and placebo arms, respectively); and had a measurable disease (71.3% and 73.5% in the abemaciclib and placebo arms, respectively). Approximately 60% of the patients in each arm had received a prior adjuvant or neoadjuvant chemotherapy. At the baseline, 70.9% of patients in the abemaciclib + fulvestrant arm and 66.8% of those in the placebo + fulvestrant arm had received a prior AI.[6,7,9]

Efficacy (Endocrine-Resistant)

The primary efficacy endpoint was investigator-assessed PFS (according to RECIST version 1.1). Key secondary end points included ORR, duration of response, OS and CBR.[7,9]

Progression-Free Survival (PFS) (Endocrine-Resistant)

At the 14-Feb-2017data cut-off date, after a median follow-up duration of 19.5 months, a total of 222 patients (49.8%) in the abemaciclib + fulvestrant arm and 157 patients (70.4%) in the placebo + fulvestrant arm had a PFS event.[7,9] The median PFS was 16.4 months with abemaciclib + fulvestrant and 9.3 months with placebo + fulvestrant (hazard ratio [HR] = 0.55; 95% confidence interval [CI] 0.45, 0.68; P < 0.001). The results of the blinded central analysis was consistent with those of the primary analysis (HR = 0.460; 95% CI 0.363, 0.584; P < 0.001). The PFS benefit was maintained across the pre-defined patient subgroups.[7,9]

Overall Survival (OS) (Endocrine-Resistant)

At the 14-Feb-2017 data cut-off date, OS results were immature, with a total of 133 deaths (85 deaths [19.1%] in the abemaciclib + fulvestrant arm and 48 deaths [21.5%] in the placebo + fulvestrant arm). The median OS was not reached in neither of the arms.[7,9] The final OS analysis is planned to be performed after occurrence of 441 death events.

Objective Response Rate (ORR) (Endocrine-Resistant)

As of the 14-Feb-2017 data cut-off date, ORR was reported to be 35.2% (95% CI 30.8%, 39.6%) in the abemaciclib + fulvestrant arm and 16.1% (95% CI 11.3%, 21.0%) in the placebo + fulvestrant arm (p<0.001).[7,9] For patients with measurable disease, ORR was 48.1% (95% CI 42.6%, 53.6%) in the abemaciclib + fulvestrant arm versus 21.3% (95% CI 15.1%, 27.6%) in the placebo + fulvestrant arm (P < 0.001).[7,9] The median time to response was estimated to be 3.7 months (interquartile range [IQR] 1.7, 16.9) with abemaciclib + fulvestrant and 4.0 months (IQR 1.9, 14.7) with placebo + fulvestrant.[7]

Clinical Benefit Rate (CBR) (Endocrine-Resistant)

CBR was a secondary endpoint in the MONARCH 2 trial and was defined as response (CR or PR) or prolonged stable disease (≥6 months) according to the RECIST version 1.1.[9] At the 14-Feb-2017 data cut-off date, CBR was 72.2% (95% CI 68.0%, 76.4%) in the abemaciclib + fulvestrant arm and 56.1% (95% CI 49.5%, 62.6%) in the placebo + fulvestrant arm (P < 0.001). Best response of prolonged stable disease was lower in the abemaciclib + fulvestrant arm (9.0%) than that in the placebo + fulvestrant arm (20.2%).[7]

Quality of Life (Endocrine-Resistant)

No peer-reviewed publications reporting on the quality of life data from the MONARCH 2 trial were identified in this pCODR review. The following data has been extracted from a conference abstract and its related poster presentation that was provided by the Submitter:

Treatment with abemaciclib + fulvestrant delayed the median time to worsening of pain by approximately five months (16.8 months in the abemaciclib arm versus 11.9 months in the placebo arm) However, this difference was not statistically significant (HR= 0.900; 95% CI 0.707, 1.145; p=0.40).[10]

When compared to placebo + fulvestrant, abemaciclib + fulvestrant resulted in a statistically significant worsening in the following symptoms from baseline: nausea and vomiting (mean change = 3.42; 95% CI 1.68, 5.15; p<0.001), appetite loss (mean change = 5.31; 95% CI 2.49, 8.13; p<0.001), and diarrhea (mean change = 24.64; 95% CI 21.58, 27.71; p<0.001). There was also a clinically meaningful (≥10 points) difference between the two groups in terms of change from the baseline in diarrhea score, favoring placebo.[10] More details can be found in Section 6.

Harms (Endocrine-Resistant)

As of the 14-Feb-2017 data cut-off date, after a median follow-up of 19.5 months, 98.6% of patients in the abemaciclib + fulvestrant arm and 89.2% of those in the placebo + fulvestrant arm had at least one reported treatment emergent AE. The most common AEs (any grade reported by≥10% of the patients) in the abemaciclib + fulvestrant arm included: diarrhea, neutropenia, nausea, fatigue, abdominal pain, anemia , leukopenia, vomiting, headache, dysgausia, and alopecia.[6] Grade 3 and 4 treatment-emergent AEs were reported for 62.6% of patients receiving abemaciclib + fulvestrant and 23.8% of those who received placebo + fulvestrant.[6] In the MONARCH 2 trial, 22.4% of patients in the abemaciclib + fulvestrant arm and 10.8% of those in the placebo + fulvestrant arm experienced at least one SAE. The frequency of withdrawal rate due to AEs was 8.6% in the abemaciclib + fulvestrant arm and 3.1% in the placebo+ fulvestrant arm.[6] Deaths due to AEs were reported in six patients (1.4%) patients receiving abemaciclib + fulvestrant and one patient (0.4%) receiving placebo + fulvestrant.[6]

Table 1.1: Highlights of Key Outcomes in the MONARCH 2 and MONARCH 3 trials

	MONARCH 2 (Endocrine-Resistant)		Monarch 3 (Endocrine-Naïve/Sensitive)†	
	abemaciclib+ fulvestrant (N= 446)	**placebo + fulvestrant (N= 223)**	**abemaciclib + AI (N= 328)**	**placebo + AI (N= 165)**
Primary Outcome				
PFS (by Investigator				
Events, n (%)	222 (49.8)	157 (70.4)	108 patients (32.9%)	86 patients (52.1%)
Median (95% CI)	16.4 (NR, NR)	9.3 (NR, NR)	Not reached	14.7
HR (95%CI)	0.55 (0.45, 0.68)		0.54 (0.41 to 0.72)	
p-value	< 0.001		0.000021	
Key Secondary Outcomes				
OS				
Events, n (%)	85 (19.1)	48 (21.5)	32 (9.8)	17 (10.3)
Median (95% CI)	Not reached	Not reached	Not reached	Not reached
HR (95%CI)	NR		NR	
p-value	NR		NR	
ORR				
All patients , % (95% CI)	35.2 (30.8, 39.6)	16.1 (11.3, 21.0)	48.2 (42.8, 53.6)	34.5 (27.3, 41.8)
p-value	<0.001		0.002	
Patients with measurable disease, % (95% CI)	48.1 (42.6, 53.6)	21.3 (15.1, 27.6)	59.2 (53.3, 65.1)	43.8 (35.3, 52.4)
p-value	<0.001		0.004	

	MONARCH 2 (Endocrine-Resistant)		Monarch 3 (Endocrine-Naïve/Sensitive)†	
CBR, % (95% CI)	72.2 (68.0 to 76.4)	56.1 (49.5 to 62.6)	72.2 (68.0, 76.4)	56.1 (49.5, 62.6)
Patient-reported outcomes/ HRQoL				
EORTC QlQ-C30, difference in mean change from baseline (p-value)				
global health status	NS		-4.36 (p=0.003)	
role functioning	NS		-4.25 (p=0.025)	
Social functioning	NS		-3.041 (p=0.047)	
Diarrhea	24.64 (21.58, 27.71; p<0.001) [clinically meaningful]		18.68 (p<0.001) [clinically meaningful]	
nausea and vomiting	3.42 (p<0.001)		2.77 (p = 0.013)	
appetite loss	5.31 (p<0.001)		4.03 (p = 0.034)	
fatigue	NS		4.96 (p=0.004)	
EORTC QlQ-BR23, difference in mean change from baseline (p-value)				
body image	NS		-5.11 (p=0.009)	
systemic therapy symptoms	5.21 (p<0.001)		4.48 (p<0.001)	
Harms Outcome, n (%)	**(N= 441)**	**(N= 223)**	**(N= 327)**	**(N= 161)**
Grade ≥3	276 (62.6)	53 (23.8)	202 (61.8)	42 (26.1)
AE [any grade]	435 (98.6)	199 (89.2)	323 (98.8)	152 (94.4)
SAE	99 (22.4)	24 (10.8)	102 (31.2)	27 (16.8)
WDAE [all AEs]	36 (8.6)	7 (3.1)	54 (16.5)	5 (3.1)
WDAE [treatments related]†	30 (6.8)	4 (1.8)	39 (11.9)	0 (0)
Death due to AE	6 (1.4)	1 (0.4)	8 (2.4)	2 (1.2)

AE = adverse event, **CI** = confidence interval, **HR** = hazard ratio, **HRQoL** = health-related quality of life, **NR** = not reported, **NS** = no statistically significant difference; **SAE** = serious adverse event, **WDAE** = withdrawal due to adverse event
*HR < 1 favours abemaciclib combination arm
† AEs related to the study treatments as judged by the investigator
† The results of primary analysis for MONARCH 3 (31-Jan-2017 data cut-off) have been presented in this table. More details on the subsequent efficacy can safety analyses are presented in text format 6.
Source documents:
Sledge J Clin Oncol 2017;[7] Kaufman ASCO 2018;[10] Goetz J Clin Oncol 2017;[2] Goetz SABCS 2018;[5] EMA Public Assessment Report (EMA/551438/2018);[6] FDA Multi-disciplinary Review (NDA 208716);[9] and FDA Multi-disciplinary Review (NDA 208855)[3]

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

From a patient's perspective, patients that completed Rethink Breast Cancer's survey considered controlling disease and extending life expectancy to be the most important results thus placing emphasis on prioritizing health outcomes over immediate concerns like reducing symptoms or managing side effects. Similarly, patients that completed the survey by CBCN expressed the willingness to try new treatments even if benefits may be as little as a six month extension of progression-free survival. Furthermore, the CBCN stated that patients want treatments that provide them with a good quality of life and concluded that based on results from the clinical trials, patients treated with abemaciclib tolerated the

treatment well. Overall, patients with metastatic breast cancer value delay in disease progression, manageable side effects, additional treatment choice and lack of detriment in quality of life.

Provincial Advisory Group (PAG) Input

PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Generalizability of data to use abemaciclib in combination with other aromatase inhibitors
- Fulvestrant is not publicly funded in any provinces for metastatic breast cancer.
- Monthly monitoring and bloodwork for neutropenia, which is not required with letrozole monotherapy

Economic factors:

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

Registered Clinician Input

Two registered clinician input submissions were provided, representing a total of five clinicians. One joint input submission on behalf of four clinicians (three medical oncologists and one oncology pharmacist) from Cancer Care Ontario as well as an individual input by a single medical oncologist, for the review of abemaciclib for patients with advanced or metastatic breast cancer was submitted. While current treatment for post-menopausal patients diagnosed with hormone receptor positive (HR) and HER2-negative metastatic breast cancer includes letrozole plus palbociclib, it was noted that abemaciclib would serve as another funded option particularly in the setting of intolerance to first line palbociclib. Furthermore, clinicians suggested that the combination of abemaciclib and fulvestrant is an option for patients with metastatic HR-positive, HER2 negative metastatic breast cancer who have progressed on previous endocrine therapy, which is considered (by the registered clinicians) as more effective than switching to another form of endocrine monotherapy.

Summary of Supplemental Questions

The following supplemental issues were identified during development of the review protocol as relevant to the pCODR review of abemaciclib for the treatment of hormone HR+/HER2– advanced or metastatic breast cancer:

Issue 1: Summary and critical appraisal of the manufacturer-submitted network meta-analysis (NMA) of interventions for loco-regionally recurrent or metastatic breast cancer patients comparable to the MONARCH 3 trial patient population (Endocrine-Naïve/Sensitive)

The Submitter provided a systematic literature review and network meta-analysis (NMA) to estimate the relative treatment effects for abemaciclib + AI (ANAS/LTZ) compared to alternative treatment options used in clinical practice within a MONARCH 3 aligned (endocrine-naïve/sensitive) patient population. The NMA was conducted in a Bayesian framework and assessed efficacy outcomes (i.e., PFS, OS, ORR, and CBR). The analysis results showed that combination CDK4&6 inhibitors and endocrine therapy regimens ABEANAS/LTZ, PAL-ANAS/LTZ and RIBO-ANAS/LTZ provided greater treatment benefit compared to single agent endocrine therapy regimens (including ANAS/LTZ) for PFS, ORR and CBR. No statistically significant differences in efficacy outcomes were found between ABE-ANAS/LTZ, PAL-ANAS/LTZ and RIBO-ANAS/LTZ. However, these NMA results should be

interpreted with caution given the heterogeneity across the studies that could impact their comparability to the MONARCH 3 trial, and the fact that adjusting for heterogeneity was not feasible due to limited data. In addition, the results of NMA for OS remained uncertain owing to immature OS data for a number of the included trials, at the time of analysis.

See section 7.1 for more information.

Issue 2: Summary and critical appraisal of the manufacturer-submitted network meta-analysis of interventions for advanced or metastatic breast cancer patients comparable to the MONARCH 2 trial patient population (Endocrine-Resistant)

The Submitter provided a systematic literature review and NMA to estimate the relative treatment effects for abemaciclib + fulvestrant compared to alternative treatment options used in clinical practice for patients progressing on or after prior endocrine therapy within a MONARCH 2 aligned patient population. The NMA was conducted in a Bayesian framework and assessed efficacy outcomes (i.e., PFS, OS, ORR, and CBR). The analysis results showed that combination therapy with ABE-FUL, PAL-FUL and EXE-EVE provided greater treatment benefit compared to FUL500 in terms of PFS, ORR and CBR. No statistically significant differences in efficacy outcomes were found between ABE-FUL and PAL-FUL. The results of NMA should be interpreted with caution given the heterogeneity across the studies that could impact their comparability to the MONARCH 2 trial, and the fact that adjusting for heterogeneity was not feasible due to limited data. The results of NMA for OS remained uncertain owing to immature OS data for a relatively large number of the included studies, at the time of analysis. See section 7.2 for more information.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.2: Assessment of generalizability of evidence for abemaciclib combination therapy in advanced or metastatic breast cancer

<table>
<tr><th colspan="5">A. Abemaciclib + AI for Endocrine-Naïve/Sensitive Advanced or Metastatic Breast Cancer</th></tr>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CBP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>ECOG performance score</td><td>The MONARCH 3 trial limited eligibility to patients with an ECOG performance status of 0-1. Patients with an ECOG PS of 2 or greater were excluded.
<table>
<tr><th>ECOG</th><th>abemaciclib + AI (n=328)</th><th>Placebo + AI (n=165)</th></tr>
<tr><td>0</td><td>192 (59%)</td><td>104 (63%)</td></tr>
<tr><td>1</td><td>136(42%)</td><td>61 (37%)</td></tr>
</table></td><td>Are the trial results (efficacy and toxicity) applicable to patients with an ECOG PS of 2 or greater?</td><td>No (see CGP conclusions statement)</td></tr>
<tr><td></td><td>Age</td><td>Fifty five percent (271/493) of the MONARCH 3 study participants were younger than 65 years old (median age 63 years).</td><td>Do the trial results apply to all adult patients?</td><td>Yes</td></tr>
</table>

A. Abemaciclib + AI for Endocrine-Naïve/Sensitive Advanced or Metastatic Breast Cancer				
Domain	**Factor**	**Evidence**	**Generalizability Question**	**CBP Assessment of Generalizability**
	Gender	All of the MONARCH 3 study participants were female.	Do the trial results apply to male patients with metastatic breast cancer?	The CGP agree that expanding the treatment indications to include the rare male patient with mBC, would be reasonable.
	Menopausal status	MONARCH 3 limited eligibility to post-menopausal women.	Are the trial results applicable to pre-or peri-menopausal women with advanced or metastatic breast cancer?	No. However, women rendered post menopausal (either chemically or surgically) would be eligible.
	Inflammatory breast cancer	Patients with inflammatory breast cancer were excluded from the MONARCH 3 trial.	Are the trial results generalizable to patients with inflammatory breast cancer?	It is standard practice from patients to start with chemotherapy since it tends to work faster and it is assumed that is why these weren't included in the trial. It would be clinically adequate to follow the trial design (i.e. not generalize to patients with inflammatory breast cancer). In the second-line or beyond setting, however, it may be reasonable if the patient has good disease control site.
	CNS metastases	Patients with an evidence or history of CNS metastases were excluded from the MONARCH 3 trial.	Are the trial results generalizable to patients with CNS metastases?	No.
	Prior therapies	MONARCH 3 excluded patients who previously received CDK inhibitors or chemotherapy.	Do the trial results apply to patients with a history of chemotherapy or CDK-inhibitor therapy in advanced/metastatic setting?	No. In terms of when (or under what circumstances/patient population) oncologists would prefer to use CDK4/6 inhibitor in the endocrine naïve setting vs. endocrine resistant setting, this will relate to timing of sequence and funding. For instance, if someone did not receive

A. Abemaciclib + AI for Endocrine-Naïve/Sensitive Advanced or Metastatic Breast Cancer				
Domain	**Factor**	**Evidence**	**Generalizability Question**	**CBP Assessment of Generalizability**
				CDK4/6 inhibitor in the first line but now progressing, then they will be considered for a CDK4/6 inhibitor at that time. If there is a choice to use CDK4/6 inhibitor in first line vs. second line, then factors such patient and physician's preferences, funding nuances may come into play.
Intervention	Dosing schedule	In the MONARCH 3 trial, abemaciclib was administered at 150 mg orally twice daily on Days 1-28 of a 28 day cycle + AI (either anastrozole 1 mg orally daily or letrozole 2.5 mg orally daily) on Days 1-28 of a 28 day cycle.	- Are there other abemaciclib + AI dosing schedules used in Canada for the initial treatment of HR+/HER2 negative advanced or metastatic breast cancer? If so, are the trial results applicable to the Canadian practice? - Could abemaciclib be used in combination with other aromatase inhibitors (other than anastrozole or letrozole)?	Dosing is adequate as per dosing schedule. abemaciclib n combination with other aromatase inhibitors (other than anastrozole or letrozole: No
	Line of therapy	The MONARCH 3 trial excluded patients with a history of endocrine therapy for locoregionally recurrent or metastatic breast cancer (exceptions: patients who received [neo]adjuvant endocrine therapy for localized disease, and those who received ≤2 weeks of non-steroidal AI in this disease setting immediately prior to screening).	Do the trial results apply to patients: - Who have progressed in prior endocrine therapy? - who are already on anastrozole or letrozole but not yet progressed? - who are already on other aromatase inhibitors but not yet progressed?	Who have progressed in prior endocrine therapy: No Who are already on anastrozole or letrozole but not yet progressed: although not included in the trial, it is reasonable provided a certain timeframe (provinces may consider this as a time limited basis)

A. Abemaciclib + AI for Endocrine-Naïve/Sensitive Advanced or Metastatic Breast Cancer				
Domain	**Factor**	**Evidence**	**Generalizability Question**	**CBP Assessment of Generalizability**
				who are already on other aromatase inhibitors but not yet progressed: No
Comparator	Standard of care	The comparator in the MONARCH 3 trial was placebo (matching with abemaciclib in the intervention arm in terms of schedule and route of administration) + AI (either anastrozole 1 mg orally daily or letrozole 2.5 mg orally daily) on Days 1-28 of a 28 day cycle. The review team identified the following treatment options as potentially relevant comparators: • endocrine therapy alone (aromatase inhibitors or selective estrogen receptor modulators) • palbociclib in combination with letrozole • ribociclib in combination with letrozole . The submitter provided an ITC that included indirect comparisons of abemaciclib + AI (anastrozole or letrozole) with alternative treatment options used in clinical practice for MONARCH 3 aligned patient (endocrine-naïve-sensitive) population. Please refer to section 7.2 for more information.	Are the results of the indirect comparisons summarized in this pCODR review generalizable to patients who may receive palbociclib (in combination with an AI), ribociclib (in combination with an AI)or endocrine therapy alone?	Refer to the CGP interpretation section for interpretation of indirect treatment comparisons
Outcomes	Appropriateness of primary and secondary outcomes	Primary outcome: PFS Secondary outcomes: ORR, Duration of response, clinical benefit rate, OS, quality of life, and safety	Were the primary and secondary outcomes appropriate for the trial design?	Yes
Setting	Countries participating in the trial	The MONARCH 2 trial was conducted in 158 centres in 22 countries. Twenty-five patients (5%) were enrolled in Canada (13 from Ontario, 12 from Quebec) from 7 sites (3 from Ontario, 4 from Quebec).	Is there any known difference in the practice pattern between other participating countries and Canada (that might impact the clinical outcomes or the resources used to	No known differences in practice patterns

A. Abemaciclib + AI for Endocrine-Naïve/Sensitive Advanced or Metastatic Breast Cancer				
Domain	**Factor**	**Evidence**	**Generalizability Question**	**CBP Assessment of Generalizability**
			achieve the outcomes)?	
AI = aromatase inhibitor**; CDK** = cyclin-dependent kinase; **CNS**= central nervous system; **ECOG** PS= Eastern Cooperative Oncology Group Performance Status; HR+/HER2: hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative; **ITC** = indirect treatment comparisons; **PFS** = progression-free survival; **ORR** = objective response rate; **OS**= overall survival				

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td colspan="5">B. Abemaciclib + Fulvestrant for Endocrine-Resistant Advanced or Metastatic Breast Cancer</td></tr>
<tr><td rowspan="4">Population</td><td>ECOG performance score</td><td>The MONARCH 2 trial limited eligibility to patients with an ECOG performance status of 0-1. Patients with an ECOG PS of 2 or greater were excluded.
<table><tr><th>ECOG</th><th>abemaciclib +fulvestrant (n=446)</th><th>Placebo +fulvestrant (n=223)</th></tr><tr><td>0</td><td>264 (59%)</td><td>136 (61%)</td></tr><tr><td>1</td><td>176(40%)</td><td>87 (39%)</td></tr></table></td><td>Are the trial results (efficacy and toxicity) applicable to patients with an ECOG PS of 2 or greater?</td><td>No (see CGP conclusions statement)</td></tr>
<tr><td>Age</td><td>Sixty three percent (424/669) of the MONARCH 2 study participants were younger than 65 years old (median age 60 years).</td><td>Do the trial results apply to all adult patients?</td><td>Yes</td></tr>
<tr><td>Gender</td><td>All of the MONARCH 2 study participants were female.</td><td>Do the trial results apply to male patients with metastatic breast cancer?</td><td>It would be biologically reasonable; however, there is no evidence to support one way or another.</td></tr>
<tr><td>Inflammatory breast cancer</td><td>Patients with inflammatory breast cancer were excluded from the MONARCH 2 trial.</td><td>Are the trial results generalizable to patients with inflammatory breast cancer?</td><td>It is standard practice from patients to start with chemotherapy since it tends to work faster and it is assumed that is why these weren’t included in the trial. It would be clinically adequate to follow the trial design (i.e. not generalize to patients with inflammatory breast cancer). In the second-line or beyond setting, however, it may be reasonable if the patient has good disease control site.</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
	CNS metastases	Patients with an evidence or history of CNS metastases were excluded from the MONARCH 2 trial.	Are the trial results generalizable to patients with CNS metastases?	No
	Prior therapies	MONARCH 2 excluded patients who previously received chemotherapy or prior treatment with everolimus or a CDK 4 and CDK 6 inhibitor in metastatic setting.	Do the trial results apply to patients with a history of chemotherapy or CDK 4/6 inhibitor therapy in advanced/metastatic setting?	No
Intervention	Dosing schedule	In the MONARCH 2 trial, abemaciclib was administered at 150 mg orally on Days 1 to 28 of a 28-day cycle + fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond.	Are there other dosing schedules used in Canada for the treatment of adult women with HR+/HER2 negative locally advanced or metastatic breast cancer whose disease had progressed on previous endocrine therapy? If so, are the trial results applicable to the Canadian practice?	Dosing is adequate as per dosing schedule.
	Line of therapy	The MONARCH 2 trial limited eligibility to patients who progressed after 1st line metastatic treatment with an anti-estrogen or AI. Patients with a history of more than one previous endocrine therapy in metastatic setting were excluded.	Do the trial results apply to patients who: – have received two or more lines of therapy in the advanced/ metastatic setting –	No
Comparator	Standard of care	The comparator in the MONARCH 2 trial was placebo (matching with abemaciclib in the intervention arm in terms of schedule and route of administration) + fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond. The review team identified the following treatment options as potentially relevant comparators: • endocrine therapy alone (aromatase inhibitors or selective estrogen receptor modulators) • palbociclib in combination with fulvestrant	Are the results the indirect comparisons summarized in this pCODR review generalizable to patients who may receive palbociclib (in combination with fulvestrant or an AI), ribociclib (in combination with an AI), AI + everolimus or endocrine therapy alone?	Refer to the CGP interpretation section for interpretation of indirect treatment comparisons

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		• palbociclib in combination with letrozole • ribociclib in combination with letrozole • aromatase inhibitor plus everolimus . The submitter provided an ITC that included indirect comparisons of abemaciclib + fulvestrant with alternative treatment options used in clinical practice for MONARCH 2 aligned patient population. Please refer to section 7.1 for more information.		
Outcomes	Appropriateness of primary and secondary outcomes	Primary outcome: PFS Secondary outcomes: ORR, Duration of response, clinical benefit rate, OS, quality of life, and safety	Were the primary and secondary outcomes appropriate for the trial design?	Yes
Setting	Countries participating in the trial	The MONARCH 2 trial was conducted in 145 centres in 19 countries. Fifteen patients (2%) were enrolled in Canada (9 from Ontario, 6 from Alberta) from 4 sites (3 from Ontario, 1 from Alberta).	Is there any known difference in the practice pattern between other participating countries and Canada (that might impact the clinical outcomes or the resources used to achieve the outcomes)?	No. Unlikely practice patterns of other countries would be significantly different, and practice pattern should be similar across provinces within Canada.

AI = aromatase inhibitor**; CDK** = cyclin-dependent kinase; **CNS**= central nervous system; **ECOG** PS= Eastern Cooperative Oncology Group Performance Status; HR+/HER2: hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative; **ITC** = indirect treatment comparisons; **PFS** = progression-free survival; **ORR** = objective response rate; **OS**= overall survival

1.2.4 Interpretation

Burden of Illness

The 2017 estimated incidence of breast cancer in Canada is 26,300, making it the most common cancer in women, with approximately 5,000 deaths, mainly due to the development of metastases.[11] Although treatable, metastatic disease is incurable, with 70% of women dying of their disease within 5 years, and median life expectancy is around 31 months.[12]

A majority of breast cancers are hormonally driven, with 65-70% being HR +, indicating potential sensitivity to endocrine therapies.[13] Most lack overexpression of the HER2 growth factor receptor, and may be associated with indolent or slowly progressive disease, particularly in the early stages. Patients presenting with HR+/HER2 negative mBC usually will have received some form of adjuvant endocrine therapy, generally an AI if postmenopausal, and tamoxifen if pre/perimenopausal. Based on clinical experience, a small minority, 5-10% presenting with de-novo metastatic disease may be endocrine therapy-naïve.

Most women presenting with HR+/HER2 negative mBC will be candidates for endocrine therapy (ET). Exceptions may be those with documented early relapse during adjuvant endocrine therapy, or with evidence of rapidly progressive visceral metastases. Usual first-line therapies include single hormonal agents such as AIs or tamoxifen in postmenopausal women, and in pre/perimenopausal women tamoxifen and/or ovarian suppression/ablation. Recently, the addition of CDK4/6 inhibitors has led to significant improvement in PFS. In the last 2 years, three CDK inhibitors (palbociclib, ribociclib and abemaciclib) have been approved by the FDA. In Canada, palbociclib is the first CDK4/6 inhibitor approved and funded in combination with letrozole for the treatment of hormone sensitive, HER2 negative mBC in the first line setting. Following progression on first line endocrine therapy, multiple treatment options remain available including the use of CDK4/6 inhibitor with Fulvestrant. Several questions remain regarding the optimal integration of CDK inhibitors in clinical practice[14] such as a) accurate identification of potential biomarkers to predict benefit, b) optimal sequence for the individual patient, and c) optimal treatment after progression on CDK inhibitors.

Need

After a pCODR recommendation (2016) and subsequent provincial reimbursement of the combination palbociclib/letrozole, an estimated 50-60% of women presenting with mBC from 2017 onward may have received palbociclib in combination with letrozole fist-line. Palbociclib is also under review in the second line setting with fulvestrant. A second CDKI (Ribociclib) in the first line setting has a position conditional recommendation from pERC but is not publicly funded yet in any jurisdiction. Abemaciclib is the third CDK inhibitor being introduced in the patient population. There are no clinical trials directly comparing the efficacy, toxicity, or HRQOL of the three CDK inhibitors. A summary table of each trial is provided below. Overall, the use of CDK inhibitors in the first-line setting has been associated with a substantial (about 10 months) benefit in PFS, while OS results are still awaited. CDK 4/6 inhibitors have a favourable safety provide, with neutropenia not associated with infections being the most common side effect. In the second line setting, the use of CDK 4/6 inhibitors has been associated with a 6-7 months PFS benefit and a HRQOL improvement. There are some differences in the safety profile among the three CDK inhibitors, with less neutropenia and more diarrhea with abemaciclib, less hepatotoxicity with palbociclib, potential for QT interval prolongation with ribociclib. Abemaciclib has shown important single-agent activity as well as potential for crossing the blood brain barrier.[2,5,7,10]

CDK4/6 inhibitors in MBC: First-line trials

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

*Patients with measurable disease

CDK4/6 inhibitors in MBC: Post-AI trials

Trial	Regimen	Phase	N	ORR*, %	PFS, Mos	HR	95% CI
PALOMA-3	Fulvestrant ± palbociclib	III	521	6 vs 10	4.6 vs 9.5	0.46	0.36-0.59

MONARCH-2	Fulvestrant + abemaciclib	III	669	21 vs 48	9.3 vs 16.4	0.55	0.45-0.68
MONALEESA-3	Fulvestrant + ribociclib	III	345	29 vs 41	12.8 vs 20.5	0.59	0.48-0.73
MONARCH-1	Abemaciclib monotherapy	II	132	20	6.0	-	-

*Patients with measurable disease

Effectiveness

Initial Therapy (Endocrine-Naïve/Sensitive)

MONARCH 3 is a double-blind, randomized phase III study of abemaciclib or placebo plus a non-steroidal aromatase inhibitor in postmenopausal women with HR-positive, HER2-negative advanced breast cancer who had no prior systemic therapy in the advanced setting. This was an international trial that globally accrued 493 patients.

In the interim PFS analysis, at median follow-up of 17.8 months the observed investigator-assessed PFS hazard ratio was 0.54 (95% CI, 0.41 to 0.72; p=.000021). The median was not reached in the abemaciclib arm and was 14.7 months in the placebo arm. Consistent PFS results were observed by independent central review. A progression-free survival benefit was demonstrated across all pre-specified subgroups. OS data were not mature at this time. So far, OS was similar between the arms, with 32 (9.8%) deaths in the abemaciclib arm and 17 (10.3%) in the placebo arm (hazard ratio, 0.97).[2]

In the final PFS analysis, the trial demonstrated a statistically significant and clinically meaningful improvement in PFS. The study met its primary end point at median follow-up of 26.7 months with an observed investigator-assessed PFS hazard ratio of 0.54 (95% CI, 0.42 to 0.70; p=.000002). The median was 28.2 months in the abemaciclib arm and was 14.8 months in the placebo arm. Consistent PFS results were observed by independent central review. A progression-free survival benefit was demonstrated across all pre-specified subgroups. OS data were not reported in the final PFS analysis publication.[4]

Progression while on Endocrine Therapy (Endocrine-Resistant)

MONARCH 2 is a global, double-blind, phase III study of women with hormone receptor-positive, HER2 negative ABC who had progressed while receiving neo-adjuvant or adjuvant endocrine therapy (ET), ≤ 12 months from the end of adjuvant ET, or while receiving fist-line ET for metastatic disease (n=713). Patients were randomly assigned to receive abemaciclib or placebo (150 mg twice daily) on a continuous schedule and fulvestrant (500 mg, per label). Abemaciclib plus fulvestrant significantly extended PFS versus fulvestrant alone (median 16.4 v 9.3 months; hazard ratio, 0.553; 95% CI, 0.449 to 0.681; P<.001). In patients with measurable disease, abemaciclib plus fulvestrant achieve an ORR of 48.1% (95% CI, 42.6% to 53.6%) compared with 21.3% (95% CI, 15.1% to 27.6%) in the control arm. OS has not been reported.

Safety

In the interim analysis in MONARCH 3, the most common grade 3 or 4 AEs were neutropenia (21.1% v 1.2%), diarrhea (9.5% v 1.2%), and leukopenia (7.6% v 0.6%). A total of 64 (19.6%) patients in the abemaciclib arm versus four patients (2.5%) in the placebo arm discontinued abemaciclib or placebo, respectively, as the result of adverse events. The most frequent cause of treatment

discontinuation was progressive disease (91[27.7%] patients in the abemaciclib arm and 86[52.1%] in the placebo arm).[2]

In the final analysis, updated safety data were reported which we consistent with the interim analysis. The most common grade 3 or more AEs were neutropenia (23.9% v 1.2%), diarrhea (9.5% v 1.2%), and leukopenia (8.6% v 0.6%). A total of 82 (25.1%) patients in the abemaciclib arm and seven (4.3%) in the placebo arm discontinued abemaciclib or placebo respectively, as a result of adverse events.[4]

Although the most common side effects experienced with abemaciclib-AI in this trial are not life threatening, they do require monitoring by an experienced health care team familiar with the toxicities associated with this combination, as a higher incidence of AEs (e.g. febrile neutropenia) may occur in an unselected non-clinical trial population. HRQOL analysis was reported in poster format. A clinically meaningful (≥ 10 points) and statistically significant worsening in diarrhea was reported in the abemaciclib + AI arm. There was a statistically significant and clinically meaningful worsening in EORTC QlQ-C30 diarrhea symptom score in abemaciclib-treated patients (mean change = 18.68; 95% CI 15.13, 22.22; p<0.001). Changes from baseline in the following EORTC QlQ-C30 symptom scores were statistically different (but not clinically meaningful) between the two study arms, all favoring the placebo arm: nausea and vomiting (mean change = 2.77; 95% CI 0.58, 4.97; p = 0.013), appetite loss (mean change = 4.03; 95% CI 0.31, 7.74; p = 0.034), and fatigue (mean change = 4.96; 95% CI 1.58, 8.35; p=0.004) (Figure 6.14B). In addition, a statistically significant worsening was observed with abemaciclib in global health status, role functioning and social functioning)(Figure 6.14A). No clinically meaningful differences were observed between the two groups in terms of EORTC QlQ-BR23 functional and symptom scales. However, statistically significant differences were observed, favoring placebo, for body image (mean change = -5.11; 95% CI -8.94, -1.29; p=0.009), and the composite score for the systemic therapy symptoms (mean change = 4.48; 95% CI 2.12, 6.83; p<0.001) (Figure 6.15).

In MONARCH 2, the most common adverse events of any grade were diarrhea, neutropenia, nausea, fatigue, and abdominal pain. These occurred at predominately grade 1 or 2 severity. Febrile neutropenia was reported in six patients in the abemaciclib arm. There was a higher incidence of infections in the abemaciclib arm (42.6%) than in the placebo arm (24.7%) regardless of relatedness; however, these infections were predominately of grade 1 to 2 severity. Serious adverse events were reported in 22.4 % of patients in the abemaciclib arm and 10.8% of patients in the placebo arm. SAEs possibly related to the study drug were reported in 8.8% of patients on the abemaciclib arm and 1.3% of patients on the placebo arm, with the most frequent being diarrhea (1.4% in the abemaciclib arm v 0% in the placebo arm). Grade 1 or 2 diarrhea occurred in 322 patients (73.0%) in the abemaciclib arm and 54 (24.2%) in the control arm. In contrast, grade 3 diarrhea was less frequent (n=59[13.4%] v n=1 [0.4%] in the abemaciclib and control arms, respectively). HRQOL analysis was reported in poster format. The primary health reported outcome was time-to-progression of pain as measured by the mBPI-sf. A Kaplan- Meier plot of time-to-progression is shown in Figure 6.6. As shown, Treatment with abemacilib + fulvestrant delayed the median time to worsening of pain was by approximately five months (16.8 months in the abemaciclib arm versus 11.9 months in the palcebo arm) However, this difference was not statistically significant (HR= 0.900; 95% CI 0.707, 1.145; p=0.40).[10] As shown in Figure 6.7, changes from baseline in the following three EORTC QlQ-C30 were statistically different between the two study arms, all favoring the placebo arm: nausea and vomiting (mean change = 3.42; 95% CI 1.68, 5.15; p<0.001), appetite loss (mean change = 5.31; 95% CI 2.49, 8.13; p<0.001), and diarrhea (mean change = 24.64; 95% CI 21.58, 27.71; p<0.001). There was also a clinically meaningful (≥10 points) difference between the two groups in terms of change from the baseline in diarrhea score.[10] No statistically significant or clinically meaningful differences were observed between the two groups in terms of EORTC QlQ-BR23 functional scales, except for systemic therapy side effects (dry mouth, eye symptoms, hair loss, hot flashes, etc.) which were

significantly worse in the abemaciclib + fulvestrant arm (mean change = 5.21; 95% CI 3.49, 6.92; p<0.001; Figure 6.8).[10]

For both initial therapy and progression while on ET, these results of the NMA should be interpreted with caution given the heterogeneity across the studies that could impact their comparability to the MONARCH 2 and 3 trials, and the fact that adjusting for heterogeneity was not feasible due to limited data. In addition, the results of NMA for OS remained uncertain owing to immature OS data for a number of the included trials, at the time of analysis.

1.3 Conclusions

The CGP concluded that there is a net overall clinical benefit to the addition of abemaciclib under the following circumstances:

1) As initial therapy with a non-steroidal AI in post-menopausal women with HR-positive, HER2 negative advanced breast cancer who had no prior systemic therapy in the advanced setting
2) In women with HR-positive, HER-2 negative ABC who had progressed while receiving neo-adjuvant or adjuvant endocrine therapy, ≤ 12 months from the end of adjuvant ET, or while receiving first-line ET for metastatic disease (excluding patients previously treated with CDK inhibitors) in combination with fulvestrant

This is based on the MONARCH 3 and MONARCH 2 trials respectively. From a clinical perspective:

a) The median PFS was significantly prolonged in the MONARCH 3 trial, the median was 28.2 months in the abemaciclib arm and was 14.8 months in the placebo arm. Of the patients enrolled, 39.8% had de novo metastatic breast cancer. This was estimated to be higher than what is typically seen in the Canadian context, however, it is in line with other trials of CDK inhibitors.
b) QOL data have not been published in peer-reviewed publication for either scenarios. It is assumed that there was no detriment in QOL in patients treated in the combination treatment group compared to placebo arms. This will also be confirmed once the peer-reviewed publication is made available.
c) OS data are immature for both trials. With sufficient follow-up, OS could be evaluated but any benefit may be confounded by post trial treatments.
d) Patients enrolled in the MONARCH 2 and 3 had an ECOG performance status of ≤ 1. Therefore, the CGP cannot conclude there is benefit in patients with a performance status of 2. As most patients in clinical practice will have a performance status of 0 or 1, the CGP felt the use of abemaciclib in appropriate patient populations should be limited to those with an ECOG PS of ≤ 1.
e) It is also important to note that the addition of abemaciclib to ET, like other CDK inhibitors, requires closer clinical monitoring compared to ET alone. Specifically, myelosuppression with neutropenia and a risk of febrile neutropenia as noted in MONARCH 2 and 3. There is also the added risk of diarrhea (up to 13.4% grade 3 reported in MONARCH 2).

f) As initial therapy, abemaciclib was combined with a non-steroidal AI (79.1% letrozole), The CGP felt the combination of abemaciclib with an AI should be limited to either anastrozole or letrozole based on the current evidence.
g) Within the Canadian context, the choice of a CDK inhibitor (Palbociclib currently funded as initial therapy) will depend on access, funding, patient / physician preference and side effect profile. In those who have not received a CDK inhibitor, the addition of abemaciclib to ET could be considered in the following scenarios:
    a. As initial therapy, in combination with a non-steroidal AI,
    b. After progression on ET: in combination with fulvestrant. The potential limitation to the use of this combination would be funding for fulvestrant and potential use of palbociclib for a similar indication (under review). There has been no direct clinical trial comparison of different CDK inhibitors in combination with fulvestrant.
    c. In patients already on ET (e.g anastrozole or letrozole or fulvestrant) but not yet progressed. Although this approach has not been formally tested in clinical trials, the GCP feels this would be acceptable if done within a reasonable time frame from the start of ET (e.g. 6 months)
    d. There is no clear guidance from the literature on the continued use of Abemaciclib at the time of oligoprogression
    e. The CGP feels that a switch between different CDK 4/6 inhibitors should be allowed in patients showing benefit but experiencing significant side effects

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 26,300 new cases and 5,000 deaths in 2017).[11] While many women diagnosed with early stage breast cancer will be cured with treatment, some women will experience a relapse of their breast cancer (metastatic spread to other organs), with an additional 5-10% of women who will present with de novo metastatic breast cancer. Advanced or metastatic breast cancer (MBC) remains incurable and is treated systematically with palliative intent. In the setting of metastatic disease, median life expectancy is approximately 2-3 years.[15]

The goals of palliative systemic therapy are threefold: to maintain or improve quality of life, to slow further progression of disease, and to prolong survival. Several systemic treatment options are available. The selection and sequencing of these therapies are dependent on several factors including the biological characteristics of the breast cancer (ER, PR, and HER-2 receptor status), patient factors, performance (functional) status, and patient preferences. Systemic options broadly include endocrine therapy, biologic/targeted therapies, and chemotherapy. These therapies are used in conjunction with bone modifying agents (e.g. bisphosphonates and RANK ligand inhibitors), radiation therapy, and supportive care (e.g. analgesics, antiemetics), depending on the clinical situation.

Approximately 75% of breast cancers over-express estrogen and / or progesterone hormone receptors.[16] In the absence of rapidly progressive disease or visceral crisis, endocrine-based therapy is usually considered first-line palliative treatment in hormone receptor (HR)-positive, HER2 negative disease, based on its efficacy and favorable toxicity profile. Commonly used options include selective estrogen receptor modulators (e.g. tamoxifen), aromatase inhibitors (e.g. anastrozole, letrozole, and exemestane), selective estrogen receptor degraders (e.g. fulvestrant), and less commonly, progesterone agents (e.g. megestrol acetate). Unfortunately, most endocrine-sensitive breast cancers inevitably develop acquired resistance to hormone-based therapy, necessitating a change in palliative treatment approach. In addition, a small proportion of patients with HR-positive disease at initial presentation does not respond to first-line endocrine therapy (ET), and are considered to have primary endocrine resistance. First-line endocrine therapy treatment failures have fueled research interest in better understanding intracellular pathways and mechanisms involved with both acquired and primary endocrine resistance, in order to circumvent these outcomes. Recent studies have expanded our knowledge related to intracellular signaling, allowing the development and usage of targeted agents (e.g. mTOR signaling pathway inhibitor and CDK4/6 inhibitors).

2.2 Accepted Clinical Practice

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

Advanced breast cancer invariably develops mechanisms of resistance to endocrine-based systemic therapy. One such mechanism involves constituent activation of the PI3K-Akt-mTOR signaling pathway.[17] Targeted agents such everolimus have been developed to block this signal transduction pathway, and have shown clinical progression free survival (PFS) benefit in combination with exemestane (aromatase inhibitor) therapy.[18] Another signaling pathway involves aberrant dysregulation of the cell division cycle. Cellular replication involves a host of tightly regulate steps, all coordinated by specialized cell cycle signaling molecules, such as cyclin-dependent kinases (CDKs), a series of small molecule serine threonine kinase enzymes that combine with their associated cyclins to regulate the passage of cells through the growth and division cycle. Studies have discovered multiple genetic mutations which activate these pathways, leading to uncontrolled growth and rapid division of malignant cells. Overcoming the inappropriate activation of CDKs has proven to be an additional therapeutic tool to limit progression of metastatic HR+ breast cancer.

Palbociclib (Ibrance, Pfizer) and ribociclib (Kisqali, Novartis) are reversible, oral, small molecule inhibitors of cyclin dependent kinases 4 and 6 (CDK4/6) which stops the progression through the cell cycle from G1/S 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 key driver of the cell cycle. A number of pre-clinical and clinical studies have demonstrated that the combination of palbociclib or ribociclib with endocrine therapies (including tamoxifen, aromatase inhibitors, or fulvestrant) are able to overcome endocrine resistance, and improve progression free survival (PFS). In addition, the combination has been found to have reasonable toxicity profile, especially when compared with standard chemotherapy. Myelosuppression with neutropenia is the most common adverse event but episodes of febrile neutropenia are very rare.[19-24]

Abemaciclib is an orally administered, potent, and selective small molecule inhibitor of CDK 4/6 administered on a twice daily continuous schedule. Abemaciclib is structurally distinct from other CDK 4/6 inhibitors and is 14 times more potent against cycle D1/CDK 4 and cycle D3/ CDK6 in enzymatic assays. In a phase 1 study, abemaciclib demonstrated activity in HR+ MBC as monotherapy and in combination with fulvestrant. MONARCH 1 is a phase II study of abemaciclib as a single agent (200 mg twice daily on a continuous schedule) in patients with hormone refractory HR+/HER2- MBC, with an overall response rate of 19.7%, median duration of response of 8.6 months, and clinical benefit rate of 42.4%.[25] Since then, Abemaciclib has been studied in 2 large RCT (MONARCH 2 and MONARCH 3).[7,26]

2.3 Evidence-Based Considerations for a Funding Population

The evidence based population suitable for consideration of abemaciclib in combination with an aromatase inhibitor or fulvestrant for the treatment of HR+ MBC would be the same population included in the MONARCH-2 and MONARCH-3 clinical trials.

This would include women with HR+, HER2 negative MBC (including non curable locally recurrent breast cancer).

MONARCH 2: any menopausal status (pre or perimenopausal women received a gonadotropin-releasing hormone agonist) with and ECOG status of 0 or 1, and adequate bone marrow and organ function. Patients were required to have disease progression while receiving neoadjuvant or

adjuvant ET, ≤ 12 months after adjuvant ET, or while receiving ET for ABC. Patients must not have received more than one ET or any prior chemotherapy for advance breast cancer (ABC). Patients were excluded if they had previously received fulvestrant, everolimus, or CDK 4/6 inhibitors; presence of visceral crisis; evidence or history of CNS metastasis. Treatment with fulvestrant + abemaciclib or placebo continued until disease progression, death, or patient withdrawal. Abemaciclib was given at 200 mg twice daily. After a review of safety data and dose reduction rates, the protocol was amended to reduce the starting dose to 150 mg twice daily.

MONARCH 3: postmenopausal with adequate organ function and ECOG status (≤ 1). Patients must not have received systemic therapy for advanced disease. Endocrine therapy in the neoadjuvant or adjuvant setting was permitted if he patient had a disease-free interval > 12 months from the completion of ET. Patients received abemaciclib (150 mg twice daily continuous, with or without food) or matching placebo plus a nonsteroidal AI (anastrozole or letrozole). Treatment continued until disease progression, unacceptable toxicity, death, or patient withdrawal for any reason.

2.4 Other Patient Populations in Whom the Drug May Be Used

Currently, the use of abemaciclib and a nonsteroidal aromatase inhibitor may be considered as optimal first-line combination endocrine-targeted therapy; the use of abemaciclib and fulvestrant should be considered as second-line combination endocrine-targeted therapy [assuming funding is made available for fulvestrant!] in those who did not receive a CDK4/6 inhibitor in the first line setting. There are no data directly comparing the efficacy and toxicity of all three CDK4/6 inhibitors, however, they appear to perform similarly. The toxicity profiles differ slightly with more GI side effects with abemaciclib.

There are no data to support the use of abemaciclib with ET in patients with brain metastases (only phase II data presented at ASCO 2017) or those with HR+ HER2+ MBC (not included in the study population). Further studies are warranted in these patient populations.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The patient advocacy groups that provided input on abemaciclib for metastatic breast cancer were Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer.

The following sources of information were used by the patient advocacy groups providing input:

Rethink Breast Cancer conducted two online patient surveys and respondents were identified through messages via Rethink Breast Cancer's mailing list as well as the Young Women's Network and partner organizations. Messages were posted on social media platforms including Facebook and Twitter as well as cancer connection and cancer survivors network online discussion boards.

- A general survey was conducted on metastatic breast cancer patients between August 2, 2018 and November 27, 2018 (N= 74). Questions related to the impact of breast cancer on the lives of patients and the effects of current treatments were outlined. The geographic location of individuals providing input for this survey is summarized in Table 3.1.
- A survey of patients with HR+, HER2- advanced or metastatic breast cancer was conducted between December 4 and December 10, 2018 (N =6). Three respondents had been treated with abemaciclib. Of these three respondents, one is a post-menopausal woman who is being treated with abemaciclib in combination with an aromatase inhibitor as initial endocrine-based therapy and two respondents are postmenopausal women with disease progression following endocrine therapy who are being treated in combination with fulvestrant.

Table 3.1- Geographic location of participants that responded to survey from August 2, 2018 and November 27, 2018

Online Survey, n=74	
Country	**Number of patients, n (%)**
Canada (across 8 Provinces)	60 (81%)
US	9 (12%)
UK	1 (1.4%)
Guyana	1 (1.4%)
Ireland	1 (1.4%)
India	1 (1.4%)
New Zealand	1 (1.4%)

The CBCN conducted two online surveys, along with a review of current studies and grey literature to identify issues that are commonly shared among women living with breast cancer.

- An online survey in 2017 and collected data from 180 Canadians living with metastatic breast cancer via CBCN's patient network, website and social media. It is unclear whether patients that completed responses to the survey have experience with the treatment under review.
- In collaboration with Rethink Breast Cancer, CBCN conducted an online survey in 2012 to patients living with metastatic breast cancer along with their caregivers. Seventy-one patients participated in the survey and 16 caregivers provided responses in the survey. None of the patients indicated experience with the treatment under review.

From a patient's perspective, patients that completed Rethink Breast Cancer's survey considered controlling disease and extending life expectancy to be the most important results thus placing emphasis on prioritizing health outcomes over immediate concerns like reducing symptoms or managing side effects. Similarly, patients that completed the survey by CBCN expressed the willingness to try new treatments even if benefits may be as little as a six month extension of progression-free survival. Furthermore, the CBCN stated that patients want treatments that

provide them with a good quality of life and concluded that based on results from the clinical trials, patients treated with abemaciclib tolerated the treatment well. Overall, patients with metastatic breast cancer value delay in disease progression, manageable side effects, additional treatment choice and lack of detriment in quality of life.

Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences patients have with metastatic breast cancer

Respondents to the general patient survey rated the impact of cancer symptoms associated with metastatic cancer on their quality of life and activities of daily living using a scale of 1 (no impact) to 5 (significant impact). The most severely reported symptom was fatigue with an average score of 3.5 (n=68) followed by bone pain with an average score of 2.7 (n=70). The ability to work was reported by respondents with the greatest impact with an average score of 3.99 (n=70) followed by their ability to sleep with a score of 3.46 (n=72).

CBCN's 2012 Metastatic Breast Cancer and Caregiver Survey assessed the physical impact of metastatic breast cancer on patients and they were asked what impact cancer related symptoms had on their quality of life. Survey results revealed 54% of patients reported that fatigue resulted in a significant or debilitating impact and 40% reported some or moderate impact. Thirty-nine percent of patients who reported that insomnia resulted in a significant or debilitating impact and 46% reported some or moderate impact. Finally, 37% of patients reported that pain resulted in a significant or debilitating impact and 44% reported some or moderate impact.

CBCN's 2017 Metastatic Breast Cancer and Caregiver Survey assessed the social impact of breast cancer (e.g., ability to care for children and dependents, socially and meaningfully participate in their community) in which patients were asked what impact living with metastatic breast cancer has had on quality of life. Survey results revealed 47% of respondents were employed full-time at the time of diagnosis, with only 12% employed full time at the time of the survey. Seventy-four percent of patients had experienced an impact on their mental health as a result of their diagnosis. Finally, 42% stated that the diagnosis had some negative impact on their finances, with 40% reporting a large negative impact on their finances

CBCN's 2012 Metastatic Breast Cancer and Caregiver Survey asked patients what impact cancer had on their quality of life. The survey results revealed that 49% of patients identified significant restrictions and 38% identified some or moderate restrictions to their ability to exercise. Forty-two percent of patients identified significant restrictions and 42% identified some or moderate restrictions to their ability to pursue hobbies and personal interests. There were 41% of patients that identified some or moderate restrictions to their ability to participate in social events and activities. Finally 22% of patients identified significant restrictions and 52% of patients identified some or moderate restrictions to their ability to spend time with loved ones.

There were other experiences identified by patients including guilt, the feeling of being a burden on caregivers, fear of death, poor body image, not knowing what functionality will be lost, fear of impact of the cancer and the loss of a parent on children, not knowing what will happen to children, the loss of support of loved ones, marital stress/loss of fidelity and affection from partner.

The following quote was shared by a patient in the 2017 Metastatic Breast Cancer and Caregiver Survey:

"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 had 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."

3.1.2 Patients' Experiences with Current Therapy for metastatic breast cancer

CBCN indicated that current treatments for metastatic breast cancer are designed to control the progression of the disease and reduce cancer-related symptoms. While types of treatment options and effectiveness vary depending on several factors (e.g., location of cancer, type of cancer, symptoms experienced), treatment options are limited to hormonal therapies and chemotherapy for hormone-receptor positive patients. The patient advocacy group also noted that there is considerable financial burden associated with living with advanced breast cancer which includes not only the loss of income during illness but also metastatic breast cancer patients can incur substantial costs associated with treatment and disease management. Findings reported by CBCN on the financial impact of breast cancer on patients identified the following:

There were 80% of breast cancer patients that reported a financial impact due to their illness, 44% of patients had used their savings and 27% had taken on debt to cover costs. CBCN's 2017 Metastatic Breast Cancer and Caregiver Survey revealed that 39% of respondents indicated that were prescribed cancer medications that weren't covered by the public health care system and 8% of respondents didn't take their medications due to the cost. There were 85% of patients that indicated they were prescribed support medications that were covered by the public health care system and 7% of respondents didn't take their medications due to the cost. Some examples of other barriers include not qualifying for insurance at work, inability to change employers due to loss of insurance and the prohibitive cost of new treatment options.

The following quote was shared by a patient in the 2017 Metastatic Breast Cancer and Caregiver Survey: *" I worry that in the future, a drug that may work for me won't be accessible to me based on the provincial formulary."*

CBCN's 2012 Metastatic Breast Cancer and Caregiver Survey assessed patient access to local resources and supports during treatment. Survey results revealed that among patients with children or other dependents, 53% indicated that there is minimal or no access to appropriate care for the loved ones when they are experiencing debilitating symptoms related to their cancer and 40% identified barriers to accessing quality care during cancer treatment.

Furthermore, patient's willingness to tolerate treatment side effects was asked in the 2012 survey. When patients were asked what level of side effects and how much impact on one's quality of life would be worth extending progression-free disease by 6 months, the message sent by patients was this assessment can only be determined by an individual patient, in this circumstance.

When patients were asked to rate the impact of different symptoms of cancer and cancer treatment, almost two-thirds of patients indicated that when it comes to fatigue, nausea, depression, problems with concentration, memory loss, diarrhea and insomnia, some or a moderate impact on one's quality of life would be considered acceptable, and approximately one quarter of patients indicated that a strong or debilitating impact would be considered acceptable.

Results from the 2012 survey found that 70% of patients indicated that when it comes to pain, some or a moderate impact on one's quality of life would be considered acceptable, and 27% of patients indicated that a strong or debilitating impact would be considered acceptable.

The 2012 and 2017 CBCN survey included open-ended questions that revealed that all women with metastatic breast cancer have the option to access new treatments that have proven efficacy. Most patients are well aware of the adverse effects of treatment up front and they want to make a personal choice that works for them.

The following quotes were shared from patients that completed the 2012 CBCN survey:

"I think patients (ESPECIALLY young patients) should be given more decision making power in terms of access to radical treatments to control disease.[…] With two small children I am determined to access any treatment that can extend my life and I hate struggling with doctors for this access."

"I believe that I would prefer to tolerate severe restrictions in the quality of my life, if it meat that I would be able to have a longer period without progression."

The following quotes were shared from patients that completed the 2017 CBCN survey:

"Accessibility to new drugs-not limiting choices."

"Always quality of life. If I am to suffer greatly then, no, that is not what I want."

Table 3.2 summarizes the treatments that all 74 respondents from the Rethink Breast Cancer's August 2018-November 2018 survey conducted by Rethink Breast Cancer had undergone since diagnosis.

Table 3.2 Treatments undergone by respondents from the Rethink Breast Cancer's August 2018-November 2018 survey

Treatment Received	Number of patients, n
Radiation therapy	41
Surgery	37
Letrozole (femara)	36
Palbociclib (taxol)	33
Paclitaxel (taxol)	25
Tamoxifen (nolvadex)	22
Capecitabine (xeloda)	20
Trastuzumab (Herceptin)	20
Pertuzumab (perjeta)	18
Docetaxel (Taxotere)	18
Fulvestrant (Faslodex)	16
Goserelin (Zoladex)	16
Exemestane (Aromasin)	13
Doxorubicin (Adriamycin)	9
Anastrozole (Arimidex)	7
Everolimus (Afinitor)	7
Cyclophosphamide (Cytoxan)	7
Fluorouracil, epirubicin and cyclophosphamide (FEC)	6
Zoledronic acid (Zometa)	5

Treatment Received	Number of patients, n
Denosumab (Xgeva)	4
Gamma knife	4
Protein-bound paclitaxel (Abraxane)	3
Lapatinib (Tykerb)	3
Leuprolide acetate (Lupron)	2
Pamidronic acid (Pamidronate)	2
Eribulin (Halaven)	2
Gemcitabine (Gemzar)	2
Olaparib (Lynparza)	2
Ribociclib (Kisqali)	2
Trastuzumab emtansine (Kadcyla)	2
Cisplatin (Platinol)	2
Zoledronic acid (Zoledronate)	1
Abemaciclib (Verzenio)	1
Dalteparin (Fragmin)	1
Vinorelbine (Navelbine)	1
Carboplatin (Paraplatin)	1
Alendronic acid (Alendronate)	1
Bazedoxifene	
Enobasarm	1
Naproxen	1
GDC-0077	1

Based on the side effects reported for these treatments on a scale of 1 (no impact) to 5 (significant impact), fatigue was the most commonly reported (90%), bone and joint pain (79%), sleep issues (70%), hair loss and menopausal issues (63%), brain fog (62%) and nausea (56%).

Similarly, when patients were asked to rate how their cancer treatments have impacted their day-to-day activities and quality of life on a scale of 1 (no impact) to 5 (significant impact), respondents indicated that the greatest impact was on their ability to work with an average score of 3.88 (n=68) followed by their ability to sleep (3.14, n=72) and their ability to concentrate (3.1, n=72).

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Experiences To Date with Abemaciclib

Three respondents from the United States have been treated with abemaciclib and are still receiving this therapy.

One postmenopausal woman indicated that she was being treated with abemaciclib in combination with fulvestrant following disease progression. The respondent reported that she was receiving abemaciclib following recurrence and had been treated with abemaciclib for 3-6 months. She had previously been treated with Nolvadex, Arimidex, Femara, Ibrance, Aromasin, Xeloda, Doxil, Navelbine, Xgeva and Zometa. Regarding treatment with abemaciclib specifically, the respondent indicated the following, *"This has been the easiest treatment I have received so far that actually worked. I could happily stay on it forever, so I'm praying that it will keep me stable for a long time."*

Another postmenopausal patient who was receiving abemaciclib in combination with fulvestrant following disease progression indicated that she was receiving third-line or higher treatment and had been treated with abemaciclib for 3-6 months. In addition, the patient stated that she had a history of treatment with Nolvadex, Arimidex, Femara, Ibrance, Afinitor, Aromasin and Xeloda.

The third postmenopausal patient, who was under treatment with abemaciclib in combination with an aromatase inhibitor as initial endocrine-based therapy, stated that she was receiving first-line treatment and had been treated with abemaciclib for less than 3 months. She had treatment experience with Nolvadex, Femara, Aromasin, Taxotere, Zometa and cyclophosphamide.

The most commonly reported side effect associated with abemaciclib therapy was diarrhea, by all three respondents. Other reported side effects included: loss of appetite, abdominal pain, nausea and gas. Patient comments about side effects include:
"*I had a tiny bit of occasional diarrhea the first couple of weeks but it went away and I've had no side-effects since, except low blood counts which have not been severe enough to affect my daily life. "*
"It's easy to take and other than the initial diarrhea has been fine."
"Verzenio 150mg bid with loperamide was too much - could not eat or drink, became dehydrated. Restarted after a 2 week break at 100mg bid: much better tolerated. Loose stool but not taking any antidiarrheal."

There was consensus among the three patients for recommending abemaciclib to other patients with advanced or metastatic breast cancer. Two patients stated the following:
"I would definitely recommend it to anyone who is eligible to take it. I also would talk to your doctor about starting the drug at a lower dose than is currently recommended, if possible. Many of the women I talk to who started at the recommended dose have problems with diarrhea, but it is possible that it may work at a lower dose without that side-effect, as it has for me."
"I would recommend this to women who want a chemo break."

While CBCN was unable to connect with Canadian patients who had experience with abemaciclib, previous surveys and submissions revealed that patients with this stage of disease should have access to many treatment options as it is a heterogeneous disease. Treatments that provide a good quality of life is also important and data from clinical trials showed that abemaciclib seemed to be well tolerated by patients.

3.3 Additional Information

No additional information was noted.

3.4 Improved Outcomes

Rethink Breast Cancer evaluated the importance of different outcomes for breast cancer treatment and patients reported responses on a scale of 1 (not important) to 5 (very important). The average score across all the listed outcomes below was over 4.4. Controlling disease and extending life expectancy were rated as the most important results suggesting that patient values prioritize health outcomes over immediate concerns like reducing symptoms or managing side effects. Please see summary of results in Table 3.3.:

Table 3.3: Importance of outcomes for breast cancer treatment

Importance of outcome	1 - not important	2	3	4	5 – very important	Average
Controlling disease (n= 73)	0.00%	0.00%	0.00%	1.37%	98.63%	4.99
Reducing symptoms (n=73)	1.37%	0.00%	13.70%	20.55%	64.38%	4.47
Maintaining quality of life (n=73)	0.00%	0.00%	1.37%	13.70%	84.93%	4.84
Managing side effects (n=73)	1.37%	1.37%	13.70%	20.55%	63.01%	4.42
Achieving NED [no evidence of disease] (n=72)	1.37%	1.37%	0.00%	6.94%	90.28%	4.83
Extending life expectancy (n=72)	0.00%	0.00%	0.00%	2.78%	97.22%	4.97

Patients were asked on a scale of 1 (will not tolerate side effects) to 10 (will tolerate significant side effects) if they would be willing to tolerate new side effects from new drugs to extend life expectancy. Respondents gave an average score of 7.66 supporting the conclusion that patient values prioritize health outcomes.

According to the CBCN, progression free survival and overall survival are considered important outcomes. Data from the phase III MONARCH 2 and MONARCH 3 trials showed that patients expect that abemaciclib in combination with fulvestrant or an aromatase inhibitor will increase their progression free survival while allowing them to live a better quality of life than if they were regulated to chemotherapy or other therapies with high toxicity profiles.

In terms of adverse events, both trials demonstrated abemaciclib was well tolerated with only approximately 1% of patients dropping out of the MONARCH 2 and MONARCH 3 trials due to side effects. The most common adverse events were diarrhea, neutropenia, nausea and fatigue. Grade 3 and 4 adverse events were able to be managed by decreasing the dosage, which mitigated patients having to stop treatment.

Patients living with metastatic breast cancer are looking to be able to access as many options as possible that will delay the progression of their disease and provide them with a good quality of life.

As patients are aware that living with advanced disease will progress with worsening symptoms until death, they are open to opportunities to trying new treatments, even if benefits may be as little as a six month extension of progression-free disease.

Patients also value quality of life when receiving treatment for metastatic disease. Patients also acknowledge the importance to have the energy to attend their children's/grandchildren's activities and to spend time with family and friends.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

Input was obtained from **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:

- Generalizability of data to use abemaciclib in combination with other aromatase inhibitors
- Fulvestrant is not publicly funded in any provinces for metastatic breast cancer.
- Monthly monitoring and bloodwork for neutropenia, which is not required with letrozole monotherapy

Economic factors:

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

Please see below for more details.

4.1 Currently Funded Treatments

Endocrine-naïve/sensitive advanced breast cancer

Various aromatase inhibitors are available for initial treatment of advanced or metastatic disease in hormone-receptor positive, HER-2 negative breast cancer. These include anastrozole, exemestane and letrozole. Palbociclib plus letrozole is also available in most jurisdictions while ribociclib as an initial endocrine-based therapy recently completed review at pCODR. PAG is seeking information comparing abemaciclib to ribociclib and palbociclib - is one better than the others and under what circumstances would abemaciclib be preferred to ribociclib or palbociclib or vice-versa?

PAG noted that the MONARCH 3 trial compared abemaciclib plus an aromatase inhibitor (anastrozole or letrozole) to an aromatase inhibitor alone. PAG is seeking information with other aromatase inhibitors.

Endocrine-resistant advanced breast cancer

PAG noted that the comparator in MONARCH-2 was fulvestrant and fulvestrant is not publicly funded in any provinces for metastatic breast cancer. PAG is seeking information on data comparing abemaciclib plus fulvestrant to currently available treatments.

PAG also noted that palbociclib-fulvestrant is currently undergoing pCODR review for patients with disease progression following endocrine therapy. PAG would like guidance on how abemaciclib-fulvestrant compares with palbociclib-fulvestrant - is one better than the others and under what circumstances would abemaciclib be preferred to palbociclib or vice-versa?

4.2 Eligible Patient Population

Endocrine-naïve/sensitive advanced breast cancer

PAG is seeking information on whether results with abemaciclib would be generalizable to pre/perimenopausal women who would be treated with LHRH agonist to induce postmenopausal status.

The MONARCH 3 trial excluded patients currently receiving or have previously received chemotherapy for locoregionally recurrent or metastatic breast cancer; PAG is seeking confirmation that these subgroups of patients would not be eligible for treatment with abemaciclib.

Endocrine-resistant advanced breast cancer

PAG recognizes that there may not be data on the use of abemaciclib plus an aromatase inhibitor (letrozole or anastrozole) in patients who have been previously treated for metastatic disease with other aromatase inhibitors but indicated there may be pressure from oncologists and patients to use abemaciclib plus an aromatase inhibitor (letrozole or anastrozole) as second-line.

Overall (endocrine-naïve and endocrine-resistant)
PAG noted that this is a large patient population.

The MONARCH 2 and 3 trials excluded patients with inflammatory breast cancer. PAG is also seeking information on whether results with abemaciclib would be generalizable to men with metastatic breast cancer.

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

- adding abemaciclib for patients who are already on an endocrine therapy (e.g., anastrozole or letrozole if endocrine-naïve or fulvestrant if endocrine-resistant) but not yet progressed
- use with other aromatase inhibitors
- switching patients who are already on other endocrine therapy but not yet progressed to abemaciclib
- switching abemaciclib with ribociclib or palbociclib for the respective indications, if patient is intolerant to one
- continuing treatment if there is oligoprogression

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 abemaciclib compared to use of chemotherapy after abemaciclib.

4.3 Implementation Factors

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 gastrointestinal-related toxicity with the addition of abemaciclib, patients will need to be seen monthly for monitoring.

Abemaciclib is dosed twice daily compared to palbociclib and ribociclib which are dosed once daily for 21 days followed by 7 days off treatment. The increased tablets of

abemaciclib daily may be less convenient for patients, however, the daily schedule without days off treatment may be easier for patients.

As abemaciclib is administered orally, chemotherapy units and chair time would not be required. As an oral drug, abemaciclib 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.

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 250mg 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. PAG noted that fulvestrant must be refrigerated and as fulvestrant comes in a large box, fridge space can become a concern. Fulvestrant requires nursing resources to administer the intramuscular injection. The volume and viscosity of fulvestrant can be a challenge for health care professionals. Patients would need monthly treatment visits, which require incremental resources over patients who receive oral endocrine therapy.

As abemaciclib 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 ribociclib and palbociclib to an aromatase inhibitor alone.

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.

- What treatments can patients receive following abemaciclib plus an aromatase inhibitor? Or following abemaciclib plus fulvestrant?
- How should everolimus plus exemestane be sequenced?
-

4.5 Companion Diagnostic Testing

None.

4.6 Additional Information

None identified.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two registered clinician input submissions were provided, representing a total of five clinicians. One joint input submission on behalf of four clinicians (three medical oncologists and one oncology pharmacist) from Cancer Care Ontario as well as an individual input by a single medical oncologist, for the review of abemaciclib for patients with advanced or metastatic breast cancer was submitted. While current treatment for post-menopausal patients diagnosed with hormone receptor positive (HR) and HER2-negative metastatic breast cancer include letrozole plus palbociclib, it was noted that abemaciclib would serve as another funded option particularly in the setting of intolerance to first line palbociclib. Furthermore, clinicians suggested that the combination of abemaciclib and fulvestrant is an option for patients with metastatic HR-positive, HER2 negative metastatic breast cancer who have progressed on previous endocrine therapy, which is more effective than switching to another form of endocrine monotherapy.

Please see below for details from the clinician input.

5.1 Current Treatment(s) for this Type of Cancer

The clinicians stated that current treatment include letrozole plus palbociclib for post-menopausal patients diagnosed with hormone receptor positive (HR) and HER2-negative metastatic breast cancer. It was also noted that fulvestrant alone would be a first line option for previously untreated metastatic breast cancer in patients without visceral disease, but fulvestrant is rarely utilized since treatment would exclude the option for first-line treatment with CDK4/6 inhibitors. Patients with metastatic HR positive, HER2-negative breast cancer who have progressed on previous endocrine therapy or have a disease-free interval ≤ 12 months from completion of endocrine therapy have limited treatment options available. Reviews currently submitted for this indication include ribociclib and fulvestrant.

5.2 Eligible Patient Population

One clinician noted the population for which reimbursement was requested aligned with clinical needs. It was further noted that because abemaciclib crosses the blood brain barrier, it may be a better option for patients with brain metastases. The clinicians providing input suggested that abemaciclib would be an alternative option to palbociclib plus letrozole, such as for intolerance as opposed to disease progression, as it affects the CDK 4 pathway differently than the CDK 6 pathway and causes less myelosuppression. Furthermore, abemaciclib and fulvestrant would be a useful treatment option for patients with metastatic HR-positive, HER2-negative breast cancer who progress on endocrine therapy (progression directly on or ≤ 12 months from the completion of adjuvant endocrine therapy), as many of these patients are currently excluded from receiving CDK4/5 inhibitor therapy. Abemaciclib and fulvestrant would also be useful for patients who choose to undergo endocrine monotherapy in the 1st line setting (tamoxifen or an aromatase inhibitor) and progress.

5.3 Relevance to Clinical Practice

Both clinician input submissions indicated experience with using the treatment under review. Having the option of another funded therapy (abemaciclib) would be helpful specifically for patients intolerant to first line palbociclib. In addition, one clinician input noted that abemaciclib has a lower risk of significant neutropenia however, abemaciclib in combination with an aromatase inhibitor does not seem to offer any unique advantages for the clinical population. The clinicians in the joint clinician input stated that abemaciclib, another CDK4/6 inhibitor offers similar efficacy to palbociclib and ribociclib. This is based on significant

improvement in progression-free survival, quality of life and a potential improvement in overall survival. Pre-menopausal women on ovarian suppression do not have access for CDK4/6 inhibitor therapy which remains an unmet need in these patients. Thus, the joint clinician input supported that all pre-menopausal women on ovarian suppression should have access to a CDK4/6 inhibitor; this was based on Monarch-2 trial and suggests a class effect of CDK4/6 inhibitors. Furthermore, clinicians suggested that the combination of abemaciclib and fulvestrant is an option for patients with metastatic HR-positive, HER2 negative metastatic breast cancer who have progressed on previous endocrine therapy, which is more effective than switching to another form of endocrine monotherapy.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

Clinicians indicated that further trials are needed to evaluate the optimal sequencing of treatment for patients with PI3K mutations given recent promising trial results in this area. While palbociclib is currently approved, combination therapy with abemaciclib and anastrozole is an alternate choice of therapy that may be offered to HR-positive, HER2 negative metastatic breast cancer patients who are:

- endocrine sensitive (for patient who have received letrozole or anastrozole is the neoadjuvant or adjuvant setting, a minimum disease-free interval of ≥12 months after stopping therapy is required for eligibility)
- who have progressed after endocrine therapy (progression directly on or ≤ 12 months from the completion of endocrine therapy).

This would replace, to some extent, the use of exemestane and everolimus in this setting. Ribociclib plus letrozole also has clinical trial evidence to support use in this population. One clinician input reinforced that abemaciclib would be another option for first line therapy and could be preferred in patients with brain metastases, or those with baseline cytopenia due to bone marrow involvement (by cancer) or residual effects of previous chemotherapy (for other cancers, or past adjuvant chemotherapy). Other endocrine options such as fulvestrant alone are not currently funded in all provinces; the other option for patients currently in this context in systemic chemotherapy.

5.5 Companion Diagnostic Testing

This section is not applicable. Hormone receptor status testing is already standard of practice in this setting.

5.6 Additional Information

One clinician indicated that abemaciclib as monotherapy demonstrates significant activity after previous aromatase inhibition and would be a valuable option in the second- or third-line treatment for select patients, however this would be considered out of scope of the current review.

5.7 Implementation Questions

Ribociclib and palbociclib in combination with an aromatase inhibitor as initial therapy for advanced or metastatic breast cancer were reviewed by the pCODR program. Palbociclib is available in some provinces and ribociclib may become an available treatment option in the future. In what clinical scenarios would abemaciclib, ribociclib or palbociclib be the preferred treatment in combination with an aromatase inhibitor as initial endocrine-based

therapy for advanced or metastatic breast cancer? Please comment on the preference considering patient preference, efficacy, safety, and administration.

Among pre-menopausal women, one clinician stated that ribociclib has the greatest evidence in this population. It was noted that abemaciclib may be preferred in the following settings: patients with brain metastases, or baseline cytopenia due to bone marrow involvement (by cancer) or residual effects of previous chemotherapy (for other cancers or past adjuvant chemotherapy). Referring to the recent trial data showing significant improvements in progression-free survival and quality of life, the clinicians providing input indicated that most HR-positive, HER2-negative metastatic breast cancer patients who are endocrine sensitive would be considered for 1st line therapy with either palbociclib, ribociclib, or abemaciclib plus an aromatase inhibitor. They noted that the individual efficacy results from these agents are similar across trials demonstrating a class effect and the side effect profiles are preferable (there are minor differences in side effects). However, the clinicians indicated that direct comparison between CDK4/6 inhibitors and MTOR inhibition (everolimus) is currently not available. The clinicians also noted that, based on the existing abemaciclib trial results, overall survival benefit in this population remain uncertain due to immature survival data. Due to the higher rates of diarrhea (grade 3/4) associated with abemaciclib (compared to either palbociclib or ribociclib), the use of loperamide is encouraged as needed. In addition, diarrhea may result in abemaciclib dose reductions.

It was expressed by the joint clinician input that palbociclib is the preferred option, given once daily dosing, fewer drug interactions, less need for cardiac monitoring, and no diarrhea issue however, they are concerned that clinicians will be forced to use abemaciclib if it is priced lower.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of abemaciclib for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2–) advanced or metastatic breast cancer:

- In combination with an aromatase inhibitor (AI) in postmenopausal women as initial endocrine based therapy.
- In combination with fulvestrant in women with disease progression following endocrine therapy. Pre- or peri-menopausal women must also be treated with a gonadotropin-releasing hormone agonist.

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

> Issue 1: Summary and critical appraisal of the manufacturer-submitted network meta-analysis of interventions for loco-regionally recurrent or metastatic breast cancer patients comparable to the MONARCH 3 trial patient population (*Endocrine-Naïve/Sensitive)*
>
> Issue 2: Summary and critical appraisal of the manufacturer-submitted network meta-analysis of interventions for advanced or metastatic breast cancer patients comparable to the MONARCH 2 trial patient population (*Endocrine-Resistant)*

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 or unpublished randomized controlled trials	Women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer Subgroup - visceral versus bone only	- abemaciclib in combination with an aromatase inhibitor in postmenopausal women as initial endocrine based therapy. - abemaciclib in combination with fulvestrant in women with disease progression following endocrine therapy. Pre- or perimenopausal	endocrine therapy alone, e.g.: • aromatase inhibitor (e.g., anastrozole exemestane letrozole) • estrogen receptor down regulator (e.g., fulvestrant) • Selective estrogen receptor modulator (e.g., tamoxifen)	Efficacy – Progression-free survival – Overall survival – Objective response rate – Duration of response – Clinical benefit** Patient-reported outcomes/ Health-

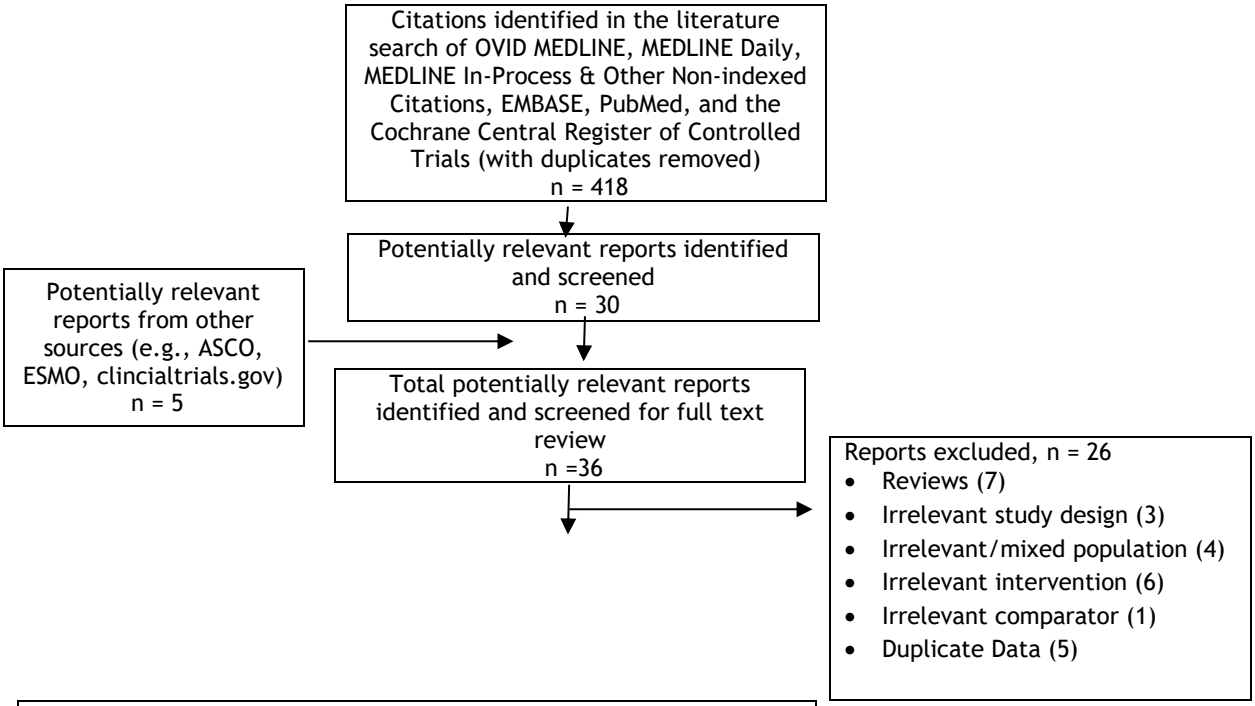
Table 6.1: Selection Criteria				
Clinical Trial Design	**Patient Population**	**Intervention**	**Appropriate Comparators***	**Outcomes**
		women must also be treated with a gonadotropin-releasing hormone agonist.	palbociclib in combination with fulvestrant palbociclib in combination with letrozole ribociclib in combination with letrozole aromatase inhibitor plus everolimus	Related Quality of Life Safety – Adverse events – Serious adverse events – Withdrawal due to adverse events Adverse event of special interest: – Cardiovascular
**Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)* ***Defined as the sum of complete and partial response and stable disease for 6 months or more.*				

6.3 A) Results for Endocrine-Naïve/Sensitive HR+ HER2- advanced or metastatic breast cancer

6.3.1 A) Literature Search Results (Naïve/Sensitive and Endocrine-Resistant)

Of the 35 potentially relevant reports identified, ten reports were included in the pCODR systematic review[2-10,27] and 26 reports were excluded. Studies were excluded because they were review articles[28-34] or irrelevant study types,[35-37] included irrelevant or mixed populations,[38-41] used an irrelevant intervention,[25,35,42-45] or included an irrelevant comparator[46]. Conference abstracts and journal articles reporting duplicate data from the included full articles were also excluded.[47-51] Figure 6.1 illustrates the PRISMA flow diagram for the study selection process. The Submitter provided feedback on the initial recommendation disagreeing with the pERC's initial recommendation for abemaciclib + NSAI in the naïve/sensitive setting. Within their feedback, the Submitter made a reference to a pooled post-hoc subgroup analysis.[52] The Methods team confirms that this reference was captured in the literature search; however, it was excluded in the initial screening phase because it was a pooled analysis of data from MONARCH 2 and MONARCH 3 trials, which used different inclusion criteria and abemaciclib combinations.

Figure 6.1: PRISMA Flow Diagram for Inclusion and Exclusion of Studies



Five reports presenting data from two clinical trials

MONARCH 2 (Endocrine-Resistant)
- Sledge J Clin Oncol 2017[7]
- Kaufman ASCO 2018[10]

MONARCH 3 (Endocrine-Naïve/Sensitive)
- Goetz J Clin Oncol 2017[2]
- Goetz SABCS 2018[5]
- Johnston NPJ Breast Cancer 2019[4]

Five reports identified and included from other resources:
Endocrine-Resistant
- ClinicalTrials.gov/NCT02107703[8]
- FDA Multi-disciplinary Review (NDA 208716)[9]

- EMA Public Assessment Report (EMA/551438/2018)[6]

Endocrine-Naïve/Sensitive

- ClinicalTrials.gov/NCT02246621[27]
- FDA Multi-disciplinary Review (NDA 208855)[3]
- EMA Public Assessment Report (EMA/551438/2018)[6]

Note: Additional data related to the MONARCH 2 and MONARCH 3 were also obtained through requests to the Submitter by pCODR[53]

6.3.2 A) Summary of Included Studies (Endocrine-Naïve/Sensitive)

6.3.2.1A) Detailed Trial Characteristics (Endocrine-Naïve/Sensitive)

One phase III, randomized, placebo-controlled trial evaluating the effect of abemaciclib in combination with an AI as initial endocrine therapy in postmenopausal women was identified. Characteristics of the MONARCH 3 trial are summarized in Table 6.2.

Table 6.2: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: MONARCH 3 (I3Y-MC-JPBM)[2,5 4] NCT02246621[27] **Characteristics** : global randomized (2:1 ratio), double-blind, placebo-controlled, phase III **N randomized**: 328 (abemaciclib), 165 (placebo) **N treated** (≥1 dose): 326 (abemaciclib), 162(placebo) Number of centres and number of countries: 158 centres in 22 countries Patient Enrolment Dates: 18-Nov-2014 to 11-Nov-2015 Data cut-off dates: 31-Jan-2017 Final Analysis: PFS - 03-Nov-2017 OS - to be performed after 315 OS events Funding: Eli Lilly	<u>Key Inclusion Criteria:</u> • ≥ 18 years of age • Female, postmenopausal† • HR+, HER2- advanced or metastatic breast cancer • ECOG performance status ≤ 1. • Measurable disease (by RECIST v1.1) or non-measurable bone-only disease • Locoregionally recurrent or metastatic disease not amenable to curative surgery or radiation therapy <u>Key Exclusion Criteria:</u> • prior treatment with everolimus, or CDK 4, 6 inhibitors • prior (neo)adjuvant endocrine therapy with a disease-free interval ≤12 months from completion of treatment • presence of visceral crisis, lymphangitic spread, CNS metastasis, or inflammatory breast cancer • Currently receiving or have previously received chemotherapy for locoreginal or metastatic breast cancer	<u>Intervention</u>: ‡ abemaciclib + AI abemaciclib 150 mg orally twice daily on Days 1 to 28 (28-day cycles) + anastrozole 1 mg orally daily or letrozole 2.5 mg orally daily on Days 1 to 28 <u>Comparator</u>: ‡ Placebo + AI placebo orally twice daily on Days 1 to 28 (28-day cycles) + anastrozole 1 mg orally daily or letrozole 2.5 mg orally daily on Days 1 to 28	<u>Primary:</u> • PFS (Investigator-assessed) <u>Secondary:</u> Efficacy • ORR (CR, PR) • DoR • CBR • OS Safety • AEs • SAEs • WDAEs <u>Other:</u> • PROs /HrQoL • Bioanalytical • Pharmacokinetic • Pharmacodynamics

AE = adverse event; **AI**; aromatase inhibitor; **CBR** = clinical benefit rate; **CNS** = central nervous system; **CR** = complete response; **DoR** = duration of response; **ECOG** = Eastern Cooperative Oncology Group; **HER2-** = human epidermal growth factor receptor 2-negative ; **HR+** = hormone receptor positive; **HrQoL** = health-related quality of life; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; PR = partial response; PROs = patient-reported outcomes; **RECIST** = Response Evaluation Criteria in Solid Tumors; **SAE**= serious adverse event; **WDAE** = withdrawal due to adverse events

† Postmenopausal status was defined by: age ≥ 60 or; age ≤ 60 and amenorrhea for ≥12 months with FSH + estradiol in postmenopausal range; or prior bilateral oophorectomy.

‡ The choice of AI (i.e., anastrozole or letrozole) was determined by the investigator and patients were to remain on the same AI throughout the study.

Table 6.3: Select quality characteristics of included studies of abemaciclib in women with HR+ HER2- advanced breast cancer (Endocrine-Naïve/Sensitive)

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
MONARCH 3	Abemaciclib + AI vs placebo + AI	PFS (investigator-assessed)	450	493	Stratified randomization (2:1 ratio) interactive Web response system	Yes interactive Web response system	Yes Placebo-controlled	Yes	No	No	Yes

a) Trials (Endocrine-Naïve/Sensitive)

Trial design

MONARCH 3 was a phase III, multi-centre, randomized, double-blind, placebo-controlled study of abemaciclib or placebo plus a nonsteroidal aromatase inhibitor (AI) in postmenopausal women with HR+/HER2− advanced or metastatic breast cancer who had not received any previous systemic therapy in the advanced/metastatic setting. The study was conducted in 158 centres in 22 countries. Eligible patients were randomized to receive abemaciclib + AI (anastrozole or letrozole per physician's choice) or placebo + AI. All drugs were orally administered on a daily basis during each 28-day cycle.[2,3]

More details about the trial design are provided below.

Randomization and treatment concealment

Randomization was performed using a centralized interactive web-based randomization system. Patients were randomized into abemaciclib + AI or placebo + AI arms in a 2:1 ratio. Randomization was stratified based on two factors:[2,3]

- nature of disease (visceral, bone only, or other); and
- prior (neo)adjuvant therapy (AI, no endocrine therapy, or other).

The study was double blind. Blinding of study participants and investigators was performed through the use of placebo capsules that matched abemaciclib capsules. A small number of Lilly personnel were able to see the randomization table and study assignments prior to study completion. Patients were to remain blinded until the final OS analysis.[3]

Blinding codes could be broken in case of need for reasons of patient safety; or after a patient discontinued treatment due to disease progression, if deemed essential for the selection of the patient's next treatment regimen. The Lilly clinical research physician was required to be consulted prior to unblinding. If the investigator or patient became unblinded, the patient was to transition to post discontinuation follow up.[3]

Study endpoints and disease assessments

The primary endpoint of the study was investigator-assessed progression-free survival (PFS), defined as the time from randomization to disease progression (according to RECIST version 1.1) or death for any reason.[2,3]

Key secondary end points included:[2,3]

- Objective response rate (ORR) defined as the proportion of patients with a complete response (CR) or partial response (PR)
- Duration of response (DoR), defined as the time from CR or PR until disease progression or death
- Clinical benefit rate (CBR), defined as CR or PR or stable disease (SD) of ≥24 weeks duration
- Overall survival (OS), defined as the time from randomization to death from any cause
- Safety and tolerability

Other secondary end points included quality of life measures and pharmacokinetics. The trial also included the exploratory endpoint of change in tumor size.[3]

After completing study screening, follow up visits were performed on Day 1 of each 28-day cycle. Tumor assessment (breast MRI, CT scan or MRI of the chest, abdomen, and pelvis) were performed on Days 21-28 of Cycle 2, and every second cycle thereafter through Cycle 18, and on Days 21-28 of every third cycle beyond Cycle 18. In the presence of any evidence of clinical progression, imaging was to be performed within 14 days of that. Bone scintigraphy was conducted on day 21-28 of every sixth cycle starting with Cycle 6. For patients with bone lesions identified at baseline, X-ray, CT scan with bone windows, or MRI were performed on day 21-28 of every second cycle starting with Cycle 2 through Cycle 18 and every third cycle thereafter. For patients with new lesions identified by post-baseline scintigraphy, targeted assessment with x-ray, CT scan with bone windows, or MRI needed to be performed to confirm findings. In the event of RECIST-defined disease progression, the study drug was discontinued.[3]

Patient-reported outcomes (PRO data) were collected using the EORTC QLQ-C30 questionnaire, EORTC QLQ-BR23 (breast) questionnaire, and the health status score from EQ-5D-5L. PRO data were collected on day 1 cycle 1, Day 1 of every second cycle beginning with Cycle 3 through Cycle 19, and on Day 1 of every third cycle after Cycle 19.[3]

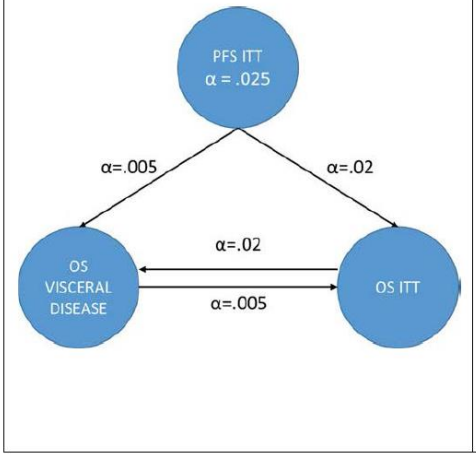
Statistical analysis

Sample size calculation

The MONARCH 3 trial was designed to 450 patients. The sample size calculation was event-driven. A total of 240 PFS events would be required for the final PFS analysis to provide approximately 80%power, assuming a HR of 0.67 at a one-sided α of 0.025. A single interim look for PFS was planned to be conducted after 189 PFS events had occurred. A positive study at the interim ((stopping rule) required a HR < 0.56 and a two-sided P < 0.0005.[2,3]

A 4-look approach was planned for the analysis of OS data, with an alpha spending plan that is shown in Figure 6.2. There is a 2% alpha allocation for OS in the ITT population and 0.5% allocation for alpha in the visceral disease population. Alpha was to be shared between the two OS endpoints, using a standard alpha gatekeeping plan.[3,6]

Figure 6.2: Alpha Spending Plan for Overall Survival



Test	Node α at Analysis	Nominal Significance Level				
		Interim PFS Analysis	Final PFS Analysis	189 OS events	252 OS events	Final OS analysis
1. Initial Graph						
PFS	0.025	0.00025	.0249993	n/a	n/a	n/a
2. Graph following signficant PFS result						
VIS OS	0.005	1*10^-9	3*10^-7	.0003	.0016	.0045
ITT OS	0.020	2*10^-9	2*10^-5	.0027	.0085	.0171
3. Graph following significant PFS and VIS OS result						
ITT OS	0.025	7*10^-9	4*10^-5	.0038	.0110	.0211
4. Graph following significant PFS and ITT OS result						
VISC OS	0.025	7*10^-9	4*10^-5	.0038	.0110	.0211

Source: EMA Public Assessment Report (EMA/551438/2018), page 59/133[6]

Efficacy analyses

The primary analysis of investigator-assessed PFS was performed on the ITT population, which included all randomized patients. An additional sensitivity analysis was performed to assess PFS by a full, blinded independent central review.[2]

PFS was analyzed using a log-rank test stratified by metastatic site and prior neoadjuvant or adjuvant endocrine therapy. Stratified tests using the Cochran-Mantel-Haenszel test were used to compare response rates between the treatment arms. Unless otherwise stated, all hypothesis tests were performed at the two-sided 0.05 statistical significance level, and all confidence intervals were estimated at a 95% confidence level exploratory subgroup analyses were performed on subgroups pre-specified in the protocol and on subgroups identified in the literature.[2,3]

Safety analysis

Safety was assessed in all patients who received at least one dose of study drug (i.e., the safety population). Safety and tolerability of abemaciclib was graded using the CTCAE (version 4.03), and the results were reported descriptively.

Treatment emergent AEs were defined as any AE beginning between the day of the first dose and 30 days after the last dose of any study drug (or any time, if they were serious and related to study treatment), or any pre-existing condition that increased in CTCAE grade between the day of the first dose and 30 days after the last dose of study drug. A serious AE was any AE during the study that resulted in death, initial or prolonged hospitalization, a life-threatening experience, persistent or significant disability, congenital anomaly or birth defect, or was considered significant for any other reason.[3]

Patient-reported outcomes analyses

Patient reported outcomes (PROs) were collected for the MONARCH 3 study using the EORTC QLQ-C30 and Breast Cancer EORTC QLQ-BR23, and EQ-5D-5L. PROs were collected on day 1 cycle 1 and then day 1 of every second cycle, cycle 2; then every second cycle starting with cycle3 through cycle 19; and every third cycle thereafter.[3,5]

Changes from the baseline scores for EORTC-QLQ-C30 and EORTC QLQ-BR23 scales and single item measures were evaluated and longitudinal regression models, controlling for the baseline EORTC values, were used for the estimation of between-group differences in change from baseline. Clinically meaningful differences from the baseline in EORTC scales were defined as ≥10 points change on a 0-100 scale. The statistical significance was set at $\alpha \leq 0.05$.[5]

Note: no peer-reviewed publications reporting on the quality of life data from the MONARCH 3 trial were identified in this pCODR review. Data presented in this pCODR report was taken from a conference abstract and its related poster presentation that was provided by the Submitter.[5]

Protocol amendments

The Monarch 3 trial had two major protocol amendments:[3]

Amendment (A) [13-Nov-2015): updated the dosing guidance for cases of hematological toxicity and diarrhea, provided guidance on the use of blood cell growth factors, and clarified supportive management of diarrhea and advice regarding co-administered drugs with narrow therapeutic margins

Amendment (B) [16-Dec-2016): removed one of two planned interim analyses for PFS and set the stopping boundary to the boundary recommended by the U S Food and Drug Administration (FDA).[3]

b) Populations (Endocrine-Naïve/Sensitive)

Eligibility criteria[2,3,6]

Eligible patients were post-menopausal women aged ≥18 years who met the following key inclusion criteria:

- Locoregional or metastatic breast cancer not amenable to curative surgical resection or radiotherapy
- ECOG performance score ≤ 1
- Estrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive tumor by immunohistochemistry (IHC) according to American Society of Clinical Oncology (ASCO) guidelines
- HER2-negative tumor by IHC or in-situ hybridization according to ASCO guidelines
- Measurable disease by RECIST (version 1.1), or non-measurable bone-only disease (i.e., blastic, lytic, or mixed)
- Relapse/progression while receiving or within 1 year of completing (neo) adjuvant endocrine therapy, no subsequent endocrine therapy OR relapse after 1st line metastatic treatment with an anti-estrogen or AI, no chemotherapy in the metastatic setting.
- Postmenopausal status due to surgical/natural menopause required ≥1 of the following criteria:
    - Prior bilateral oophorectomy
    - Age ≥60 years
    - Age <60 and amenorrheic for at least 12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and FSH and estradiol levels in the postmenopausal range
- No prior systemic therapy for advanced disease
- Adequate organ function based on protocol-defined criteria

Patients were excluded from the study if they had at least one of the following criteria:

- Presence of visceral crisis or lymphangitic spread, evidence or history of central nervous system (CNS) metastasis, inflammatory breast cancer
- Currently or previously received endocrine therapy for locoregionally recurrent or metastatic breast cancer. A patient may be enrolled if she received (neo)adjuvant endocrine therapy for localized disease. Additionally, a patient may be enrolled if she received ≤2 weeks of non-steroidal AI in this disease setting immediately prior to screening
- previous (neo)adjuvant endocrine therapy with a disease-free interval ≤12 months from completion of treatment
- Prior treatment with fulvestrant, everolimus or CDK4/6 inhibitor, initiated bisphosphonates or RANK-L targeted agent <7 days prior to randomization.
- A history of a major surgery within 14 days prior to randomization

Characteristics of the study population

A total of 493 patients were included in the MONARCH 3 trial, with 328 patients in the abemaciclib + AI arm and 165 in the placebo + arm. Patients were enrolled from 158 centres in 22 countries.[2]

Baseline demographic and disease characteristics of the ITT population are presented in Table 6.4.As shown, the baseline demographic and disease characteristics were well balanced between the study arms. All 493 enrolled patients were female and post-menopausal, with the median age of 63 years (range 32 to 88). The majority of patients were White (56.7%, and 61.8% in the abemaciclib and placebo arms, respectively) or Asian (31.4%, and 27.3% in the abemaciclib and placebo arms, respectively); and had a measurable disease (81.4% , and 78.8% in the abemaciclib and placebo arms, respectively). Prior treatments were also well-balanced between the two study arms. Approximately 40% of the patients in each arm had received a prior adjuvant or neoadjuvant chemotherapy. At the baseline, 25.9% of patients in the abemaciclib + AI arm and 30.3% of those in the placebo + AI arm had received a prior AI.[2]

Table 6. 4: patient and disease characteristics of the study population in the MONARCH 3 trial

Table 1. Patient and Disease Baseline Characteristics

Variable	Abemaciclib Plus Nonsteroidal AI	Placebo Plus Nonsteroidal AI
No. of patients	328	165
Median age, years (range)	63 (38-87)	63 (32-88)
Race, No. (%)*†		
White	186 (56.7)	102 (61.8)
Asian	103 (31.4)	45 (27.3)
Other	11 (3.4)	7 (4.2)
ECOG performance status, No. (%)		
0	192 (58.5)	104 (63.0)
1	136 (41.5)	61 (37.0)
Disease setting, No. (%)‡		
De novo metastatic	135 (41.2)	61 (37.0)
Metastatic recurrent	182 (55.5)	99 (60.0)
Locoregionally recurrent	11 (3.4)	5 (3.0)
Progesterone receptor status, No. (%)§		
Positive	255 (77.7)	127 (77.0)
Negative	70 (21.3)	36 (21.8)
Metastatic site, No. (%)‡		
Visceral	172 (52.4)	89 (53.9)
Bone only	70 (21.3)	39 (23.6)
Other	86 (26.2)	37 (22.4)
Prior neoadjuvant or adjuvant chemotherapy, No. (%)		
Yes	125 (38.1)	66 (40.0)
No	203 (61.9)	99 (60.0)
Prior endocrine therapy, No. (%)		
None	178 (54.3)	85 (51.5)
AI	85 (25.9)	50 (30.3)
Other endocrine therapy	65 (19.8)	30 (18.2)
Treatment-free interval, No. (%)‖		
< 36 months	42/150 (28.0)	32/80 (40.0)
≥ 36 months	94/150 (62.7)	40/80 (50.0)
Unknown	14/150 (9.3)	8/80 (10.0)
Measurable disease, No. (%)		
Yes	267 (81.4)	130 (78.8)
No	61 (18.6)	35 (21.2)
No. of organ sites, No. (%)†		
1	96 (29.3)	47 (28.5)
2	76 (23.2)	42 (25.5)
≥ 3	154 (47.0)	75 (45.5)

Abbreviations: AI, aromatase inhibitor; ECOG, Eastern Cooperative Oncology Group.
*Race was self-reported.
†Data missing for remaining patients.
‡Percentage does not equal 100% as the result of rounding.
§Progesterone receptor status was unknown in remaining patients.
‖Treatment-free interval calculated only for patients with prior endocrine therapy.

Goetz, M.P. et al: J Clin Oncol. 35(32):3638-3646.

c) Interventions (Endocrine-Naïve/Sensitive)

Treatment Dosing Schedule[2,3]

Patients were randomized to the following two treatment arms:

- Patients in the abemaciclib + AI arm received abemaciclib 150 mg orally twice daily on Days 1-28 of a 28 day cycle combined with either anastrozole 1 mg orally daily or letrozole 2.5 mg orally daily on Days 1-28 of a 28 day cycle.
- Patients in the placebo + AI arm received placebo orally twice daily on Days 1 to 28 of a 28-day cycle combined with either anastrozole 1 mg orally daily or letrozole 2.5 mg orally daily on Days 1-28 of a 28 day cycle.

The choice of AI (anastrozole or letrozole) was determined by the investigator and patients were to remain on the same AI throughout the study. In exceptional cases the investigator may discuss a change in AI with the Lilly CRP in the absence of disease progression. The median number of cycles received, by the 07-Nov-2017 data cut-off, was 19 in the abemaciclib + AI arm and 15 in the placebo + AI arm.[4]

Dose modifications and interruptions[3]

For patients who reported significant treatment-related toxicities, dose modifications (interruptions or reductions) were permitted for abemaciclib or placebo according to pre-specified dose-adjustment procedures. There were two recommended dose adjustment schedules (150 mg to 100mg and 100mg to 50mg, all administered twice daily). Based on the United States Prescribing Information, single dose strengths are approved for letrozole and anastrozole. In special circumstances, in the absence of an evidence of progression, and in consultation with Lilly clinical research physician, a change in non-steroidal AI drug could be made. When treatment interruption was deemed necessary for one of the study drugs in the combination, treatment with the other drug could be continued.

For patients requiring dose reductions, re-escalation to a previous dose was permitted only after consultation with a Lilly clinical research physician.

Concomitant and subsequent interventions[3]

The use of megestrol acetate as an appetite stimulant was prohibited in the MONARCH 3 trial. To prevent drug interactions, the use the following drugs should be avoided or substituted: carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, rifabutin, St. John's Wort, HIV protease inhibitors, clarithromycin, itraconazole, ketoconazole, and nefazodone. Dexamethasone was permitted as a supportive care therapy where indicated, preferably for a treatment course of ≤7 days.

The most common concomitant medications during the study were analgesics, antidiarrheals (68.5% with abemaciclib versus 16.1% with placebo), analgesics (65.1% with abemaciclib versus 64.6% with placebo), bone modifying agents (46.2% with abemaciclib versus 42.2% with placebo), and anti-emetics (13.8% with abemaciclib versus 5.0% with placebo).

Table 6.5 summarizes the subsequent treatment patients received after discontinuation of abemaciclib or placebo as of the 31-Jan-2017 data cut-off date.

Table 6.5: subsequent (post-discontinuation) treatments in the MONARCH 3 trial

	Abemaciclib + NSAI N=328 n (%)	Placebo + NSAI N=165 n (%)	Total N=493 n (%)
Patients on study treatment	162 (49.4)	64 (38.8)	226 (45.8)
Patients off treatment	164 (50.0)	98 (59.4)	262 (53.1)
Systemic therapy	111 (33.8)	80 (48.5)	191 (38.7)
Chemotherapy	47 (14.3)	35 (21.2)	82 (16.6)
Endocrine therapy	84 (25.6)	60 (36.4)	144 (29.2)
Targeted therapy	22 (6.7)	25 (15.2)	47 (9.5)
Surgical Procedure	1 (0.3)	4 (2.4)	5 (1.0)
Radiotherapy	20 (6.1)	16 (9.7)	36 (7.3)

Source: FDA Multi-disciplinary Review and Evaluation (NDA 208855), Table 17, page 67[3] Data cut-off: 31-Jan-2017

d) Patient Disposition (Endocrine-Naïve/Sensitive)[3,6]

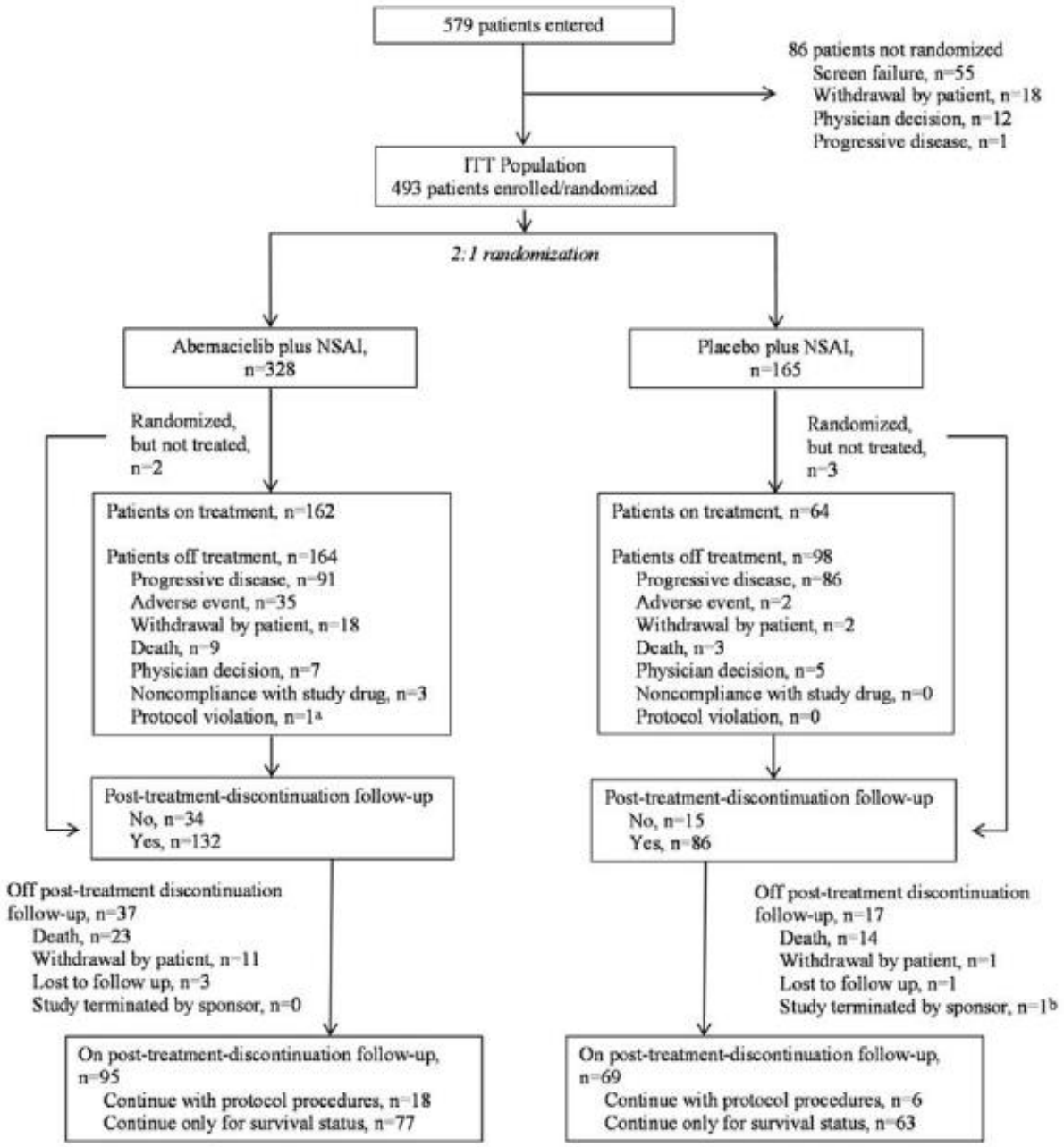
. Between November 18, 2014 and November 11, 2015, 493 patients were randomized to receive abemaciclib + AI (n = 328) or placebo + AI (n = 165). Of the 328 randomized to abemaciclib + AI, 326 were treated and of the 165 randomized to placebo + AI, 162 were treated.

At the 31-Jan-2017 data cut-off date, 162 patients were still on study treatment in the abemaciclib + AI, as compared with 64 patients in the placebo + AI arm. A total of 164 patients (50.0%) in the abemaciclib + AI arm and 98 patients (59.4%) in the placebo + AI arm had discontinued the study treatment.

At the time of final PFS analysis (03-Nov-2017 data cut-off), 125 patients in the abemaciclib + AI and 35 patients the placebo + AI arm were still on study treatment. A total of 201 patients (61.3%) in the abemaciclib + AI arm and 127 patients (77.0%) in the placebo + AI arm had discontinued the study treatment.[4]

Figure 6.3 presents the patient disposition for the MONARCH 3 trial (31-Jan-2017 data cut off). As shown, the most common reasons for study-treatment discontinuation included disease progression, AEs, and patient withdrawal.

Figure 6.3: Patient disposition in the MONARCH 3 trial



Source: EMA Public Assessment Report (EMA/551438/2018), page 60/133[6] Data cut-off: 31-Jan-2017

Protocol violations/deviations[3]

A total of 276 patients (84.1%) in the abemaciclib + AI arm and 128 patients (77.6%) in the placebo + AI arm had one or more major protocol deviations. The incidence of major protocol deviations in the MOARCH 3 trial are summarized in Table 6.6. Of note, six patients continued the study treatment after documented objective disease progression (two in the abemaciclib + AI arm and four in the placebo + AI arm). Overall, the deviations were generally well balanced between the two study arms.

Table 6.6: Protocol Deviations in the MONARCH 3 trial

Deviation Category	Abemaciclib N=328 n (%)	Placebo N=165 n (%)	Total N=493 n (%)
Patients with ≥1 major protocol deviation	276 (84.1)	128 (77.6)	404 (81.9)
Key measurements not collected properly	226 (68.9)	107 (64.8)	333 (67.5)
Incorrect stratification factors for IWRS	94 (28.7)	45 (27.3)	139 (28.2)
Improper administration of informed consent	50 (15.2)	30 (18.2)	80 (16.2)
Inappropriate handling of the investigational product	43 (13.1)	17 (10.3)	60 (12.2)
Incorrect dose adjustments	36 (11.0)	13 (7.9)	49 (9.9)
Inclusion/exclusion criteria not met	28 (8.5)	17 (10.3)	45 (9.1)
Improper treatment discontinuation	23 (7.0)	18 (10.9)	41 (8.3)
Use of prohibited concomitant medications	3 (0.9)	2 (1.2)	5 (1.0)

Source MONARCH 3 CSR page 85 with additional review of Table JPBM 10.3 on page 86

Source: FDA Multi-disciplinary Review and Evaluation (NDA 208855), Table 11, page 62[3]

e) Limitations/Sources of Bias (Endocrine-Naïve/Sensitive)

Overall, MONARCH 3 trial was a well-designed RCT, with the following steps taken to minimize potential biases:

- A double-blind study design was employed to minimize bias in the assessment and reporting of all study outcomes; study participants and investigators were blinded to the treatment assignment. However, considering the high incidence of diarrhea in the abemaciclib + AI arm (see section 3.2.2.B for detailed safety outcome results) blinding would be difficult to maintain for both patients and investigators.
- To reduce selection bias, allocation concealment was performed through a centralized interactive web-based randomization system.
- A 2:1 randomization ratio was used to increase the probability that eligible patients that would be randomized to receive abemaciclib + AI, and to increase feasibility.
- A stratified randomization procedure based on two known prognostic factors (i.e., metastatic sites, prior [neo] adjuvant therapy), was used to minimize potential imbalances between the study groups that might lead to biased results.
- Blinded independent central review (BICR) of radiological scans to reduce detection bias.
- The study adjusted for multiplicity for the analysis of key secondary outcome (i.e., OS). However, there was no formal analysis plan or alpha spending function for other secondary endpoints. Therefore, these analyses are considered descriptive.
- MONARCH 3 collected PRO data as an exploratory endpoint, using validated and reliable tools. The completion rates for all questionnaires were reported to be above 90% through Cycle 19 and above 70% during the follow up period.
- A sensitivity analysis was performed to assess PFS by a full, blinded independent central review.

The key limitations of the MONARCH 3 trial included:

- The absence of mature OS data at the time of interim analysis. Longer term follow-up is needed to determine the effect of adding abemaciclib to an AI on OS.
- The results of the subgroup analysis in MONARCH 3 trial should be interpreted with attention to the fact that the study was not powered to detect differences in the specific

subgroups. Therefore, subgroup analyses of the primary outcome are considered descriptive.

- A relative high number of patients (>80%) had one or more major protocol deviations. This proportion was higher in the abemaciclib arm (84.1%) than the placebo arm (77.6%). However, the deviations were generally well balanced between the two study groups and seem to be less likely to impact the study endpoints.

6.3.2.2A) Detailed Outcome Data and Summary of Outcomes (Endocrine-Naïve/Sensitive)

Efficacy Outcomes (Endocrine-Naïve/Sensitive)

Progression-Free Survival (PFS) *Endocrine-Naïve/Sensitive)*

PFS (investigator-assessed) was the primary endpoint in the MONARCH 3 trial. The primary analysis of PFS data was conducted on the 31-Jan-2017data cut-off date, when 194 progression events (disease progression or death) had occurred. The final analysis was performed after 240 PFS events on 07-Nov-2017.[4]

At the 31-Jan-2017data cut-off date, after a median follow-up duration of 17.8 months, a total of 108 patients (32.9%) in the abemaciclib + AI arm and 86 patients (52.1%) in the placebo + AI arm had a PFS event.[2,3] The median PFS was not reached in the abemaciclib + AI arm and was 14.7 months with placebo + fulvestrant (hazard ratio [HR] = 0.54; 95% confidence interval [CI] 0.41 to 0.72; P = 0.000021; Fig 6.4A). The results of the blinded central analysis were consistent with those of the primary analysis (HR = 0.51; 95% CI 0.36 to 0.72; P =0.000102; Fig 6.4B).[2,3]

The primary analysis of investigator-assessed PFS demonstrated a statistically significant improvement in PFS with the addition of abemaciclib to a non-steroidal AI. As the HR in the interim PFS analysis crossed the pre-determined boundary, the study was deemed successful. However, patients who had not yet progressed continued to be followed up for disease progression. A summary of the subgroup analyses of PFS, by prognostic demographic and disease characteristics, are presented in Figure 6.5.[2] As shown, the PFS benefit maintained across the pre-defined patient subgroups.

At the 07-Nov-2017 data cut-off, after a median follow-up duration of 26.73 months, 246 investigator-assessed PFS events had occurred (138 [42.1%] events the abemaciclib + AI arm and 108 [65.5%] events in the placebo + AI arm). The median PFS was 28.18 months in the abemaciclib + AI arm compared to 14.76 months in the placebo+ AI arm (HR = 0.540; 95% CI 0.418, 0.698); p = 0.000002). The results of the blinded central analysis were consistent with those of the investigator-assessed PFS analysis (HR = 0.465; 95% CI 0.339, to 0.636; p < 0.000001). In the subgroup analysis, PFS benefit maintained across the pre-defined patient.[4]

Figure 6.4: Kaplan-Meier curves of progression-free survival in the MONARCH 3 trial

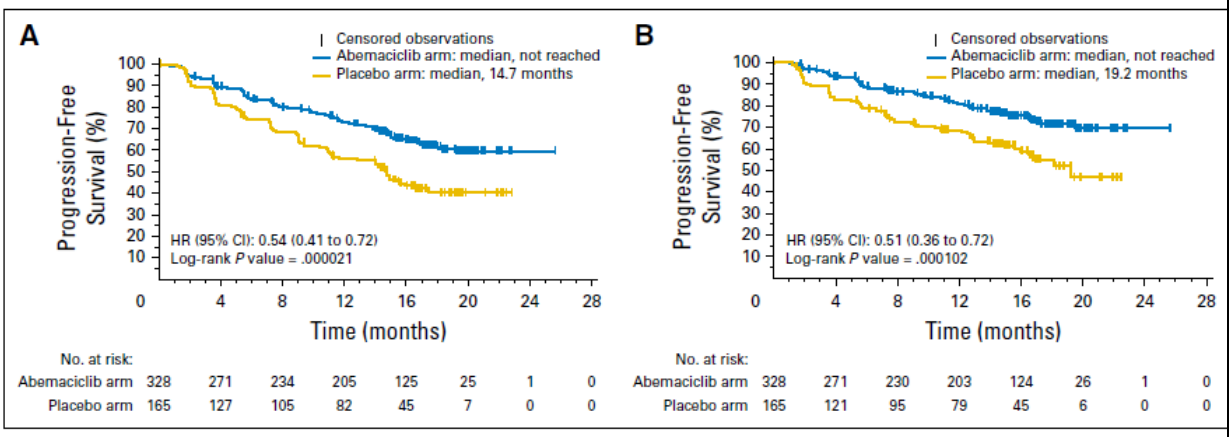
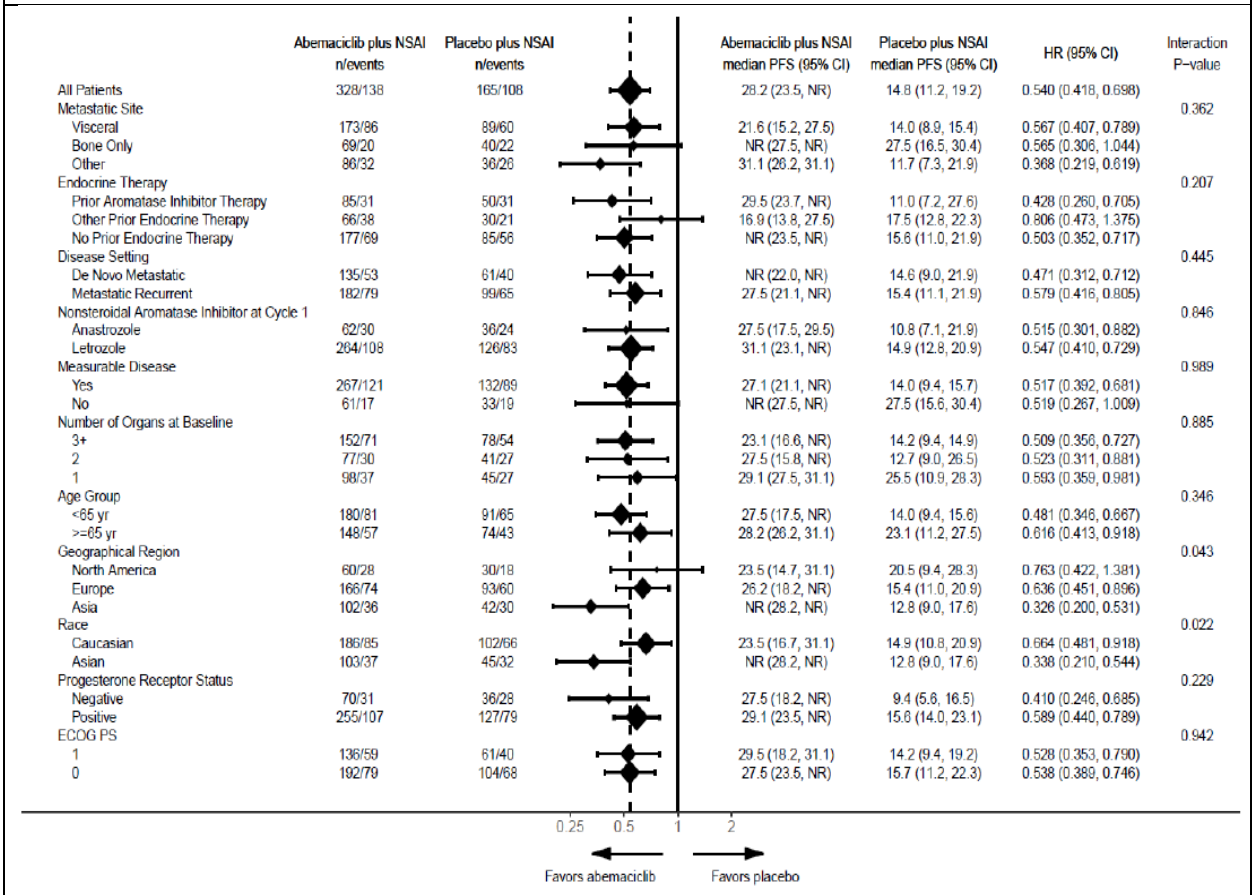


Fig 2. Progression-free survival. (A) Investigator-assessed progression-free survival in the intent-to-treat population. (B) Progression-free survival in the intent-to-trea population as evaluated by a blinded, independent central review. Abbreviations: HR, hazard ratio.

Goetz, M.P. et al: J Clin Oncol. 35(32):3638-3646.

Data cut-off: 31-Jan-2017

Figure 6.5: Preplanned PFS subgroup analyses in the MONARCH 3 trial



Source: EMA Public Assessment Report (EMA/551438/2018), page 63/133[6]
Data cut-off: 31-Jan-2017

Overall Survival (OS) *(Endocrine-Naïve/Sensitive)*

OS was a key secondary endpoint in the MONARCH 3 trial. At the 31-Jan-2017 data cut-off date, OS results were immature, with a total of 49 deaths (32 deaths [9.8%] in the abemaciclib + AI arm and 17 deaths [10.3%] in the placebo + AI arm). The median OS was not reached in neither of the arms. The results of the OS analysis are summarized in Table 6.7 and the Kaplan- Meier curves are presented in Figure 6.6).[2,3]

The final OS analysis is planned to be performed after occurrence of 315 death events.

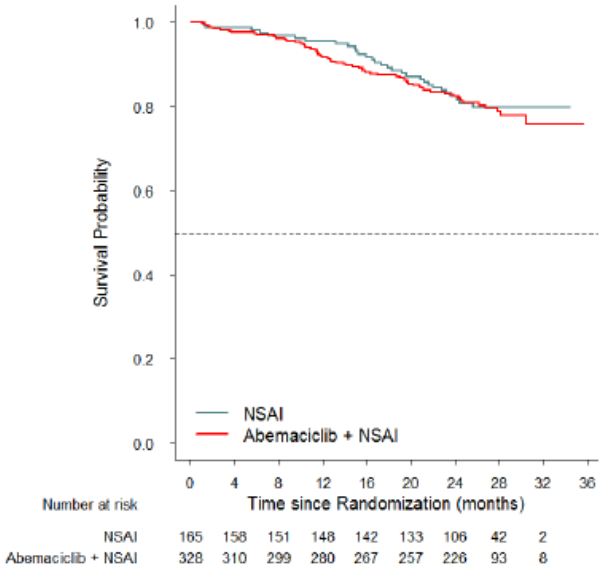
Table 6.7: Summary of OS Results from the MONARCH 3 trial

	Abemaciclib plus NSAI N = 328	Placebo plus NSAI N = 165
Events, n (%)	63 (19.2)	38 (18.2)
Censored, n (%)	265 (80.8)	127 (77.0)
Hazard ratio, estimate (95% CI)	1.06 (0.68, 1.63)	

Source: Sponsor briefing document JPBM Clinical Study Report Addendum for the Final Progression-Free Survival Analysis, data cutoff 11/3/2017.

Source: FDA Multi-disciplinary Review and Evaluation (NDA 208855), Table 23, page 72[3]
Data cut-off: 31-Jan-2017

Figure 6.6: Kaplan-Meier curves of overall survival in the MONARCH 3 trial



Source: FDA Multi-disciplinary Review and Evaluation (NDA 208855), Figure 5, page 73[3]
Data cut-off: 31-Jan-2017

Objective Response Rate (ORR) *Endocrine-Naïve/Sensitive)*

ORR was a secondary endpoint in the MONARCH 3 trial. As of the 31-Jan-2017 data cut-off date, after a median follow-up duration of 17.8 months, ORR was reported to be 48.2% (95% CI, 42.8%, 53.6%) in the abemaciclib + AI arm and 34.5% (95% CI, 27.3%, 41.8%) in the placebo + AI arm (P = 0.002). Of these responders, 135 patients (101 [63.9% in the abemaciclib + AI arm and 34 [59.6%] in the placebo + AI arm) were continuing on treatment at time of the analysis.[2] For patients with measurable disease, ORR was 59.2% (95% CI 53.3%, 65.1%) in the abemaciclib + AI arm and 43.8% (95% CI 35.3%, 52.4%) in the placebo + AI arm (P = 0.004).[2]

At the 07-Nov-2017 data cu-off date, the ORR was 49.7% (95% CI 44.3%, 55.1%) in the abemaciclib + AI arm and 37.0% (95% CI 29.6%, 44.3%) in the placebo + AI arm (p = 0.005). For the subset of 399 patients (80.9%) with measurable disease, the ORR was 61.0% (95% CI 55.2%, 66.9%) in the abemaciclib + AI arm and 45.5% (95% CI 37.0%, 53.9%) in the placebo arm (p = 0.003).[4]

Duration of Response (DOR) *Endocrine-Naïve/Sensitive)*

DOR was a secondary endpoint in the MONARCH 3 trial. At the 31-Jan-2017 data cut-off date, the median duration of response was not reached in the abemaciclib + AI arm and was 14.1 months in the placebo + AI arm.[2]

At the 07-Nov-2017 data cut-off date, the median duration of response was 27.39 months in the abemaciclib + AI arm and17.46 months in the placebo + AI arm.[4]

Clinical Benefit Rate (CBR) *Endocrine-Naïve/Sensitive)*

CBR was a secondary endpoint in the MONARCH 3 trial. At the 31-Jan-2017 data cut-off, CBR was achieved by 78.0% pf patients (95% CI 73.6%, 82.5%) in the abemaciclib + AI arm and 71.5% pf patients (95% CI 64.6%, 78.4%) in the placebo arm.[2]

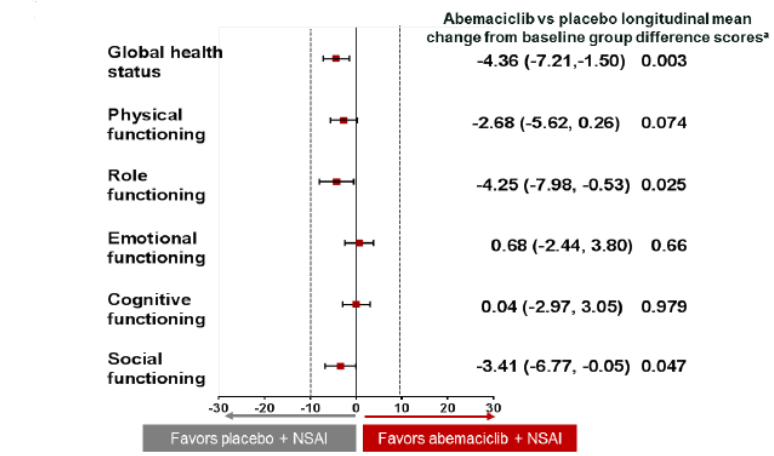
Quality of Life (Endocrine-Naïve/Sensitive)[5]

The questionnaire completion rates were ≥96% at the baseline, ≥ 90% through Cycle 19, and ≥ 70% at the follow up visits. Baseline scores were similar between the treatment arms for each questionnaire.

As shown in Figure 6.7, a clinically meaningful (≥ 10 points) and statistically significant worsening in diarrhea was reported in the abemaciclib + AI arm. There was a statistically significant and clinically meaningful worsening in EORTC QlQ-C30 diarrhea symptom score in abemaciclib-treated patients (mean change = 18.68; 95% CI 15.13, 22.22; p<0.001). Changes from baseline in the following EORTC QlQ-C30 symptom scores were statistically different (but not clinically meaningful) between the two study arms, all favoring the placebo arm: nausea and vomiting (mean change = 2.77; 95% CI 0.58, 4.97; p = 0.013), appetite loss (mean change = 4.03; 95% CI 0.31, 7.74; p = 0.034), and fatigue (mean change = 4.96; 95% CI 1.58, 8.35; p=0.004) (Figure 6.7B). In addition, a statistically significant worsening was observed with abemaciclib in global health status, role functioning and social functioning)(Figure 6.7A)

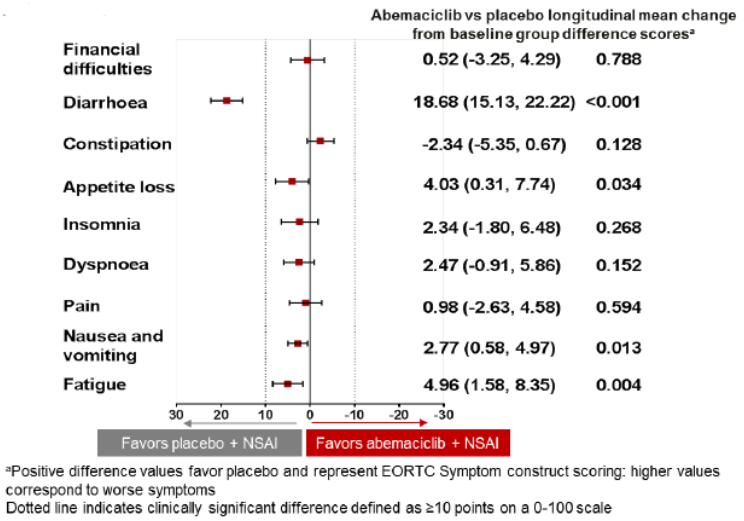
Figure 6.7: Forest plots comparing mean change from baseline in EORTC QlQ-C30 functional and symptom scales (Endocrine-Naïve/Sensitive)

A. Functioning



[a]Negative differences favor placebo and represent EORTC Functional construct scoring: higher values correspond to greater/improved function. Dotted line indicates clinically significant difference defined as ≥10 points on a 0-100 scale

B. Symptoms

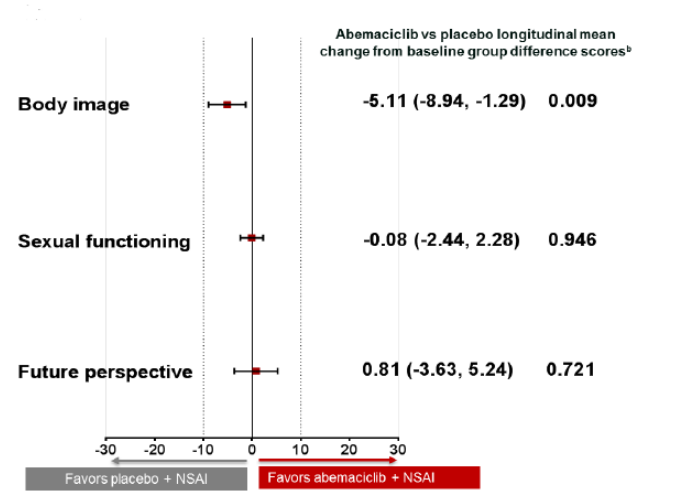


Source: Goetz et al, SABCS 2018, Poster#P6-16-01 (in manufacturer submission), Figure 1a and 1b[5]

No clinically meaningful differences were observed between the two groups in terms of EORTC QlQ-BR23 functional and symptom scales. However, statistically significant differences were observed, favoring placebo, for body image (mean change = -5.11; 95% CI -8.94, -1.29; p=0.009), and the composite score for the systemic therapy symptoms (mean change = 4.48; 95% CI 2.12, 6.83; p<0.001) (Figure 6.8).

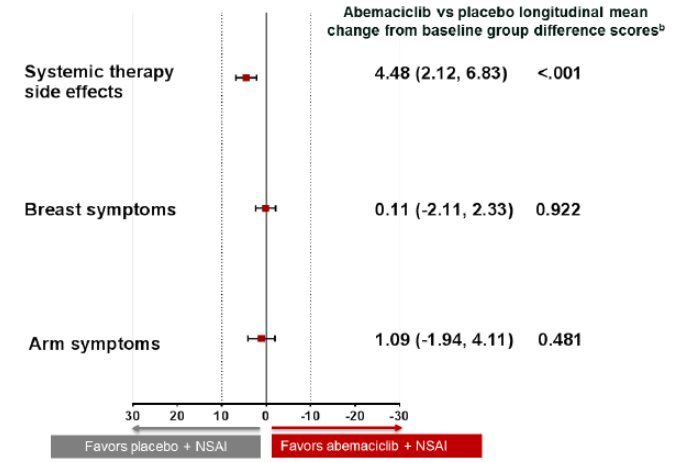
Figure 6.8: Forest plots comparing mean change from baseline in EORTC QlQ-BR23 functional and symptom scales (Endocrine-Naïve/Sensitive)

A. Functioning



[a]Functional scale for "sexual enjoyment" was not analyzed due to the preponderance of "not at all" responses with very few reports of the functional outcomes
[b]Negative differences favor placebo and represent EORTC Functional construct scoring: higher values correspond to greater/improved function
Dotted line indicates clinically significant difference defined as ≥10 points on a 0-100 scale

B. Symptoms



[a]Symptom scale for "upset by hair loss" was not analyzed due to the preponderance of "not at all" responses with very few reports of the symptom outcomes
[b]Positive difference values favor placebo and represent EORTC Symptom construct scoring: higher values correspond to worse symptoms
Dotted line indicates clinically significant difference defined as ≥10 points on a 0-100 scale

Source: Goetz et al, SABCS 2018, Poster#P6-16-01 (in manufacturer submission), Figure 4a and 4b[5]

Harms Outcomes (Endocrine-Naïve/Sensitive)[2,3]

Of the 493 patients enrolled in the MONARCH 3 trial, a total of 488 patients were treated (327 patients in the abemaciclib + AI arm and 161 patients in the placebo + AI arm) and were included in the safety analysis. The safety analysis results are summarized in Table 6.8 and the types and frequencies of AEs are provided in table 6.9.

As of the 31-Jan-2017 data cut-off date, after a median follow-up of 17.8 months, 98.8% of patients in the abemaciclib + AI arm and 94.4% of those in the placebo + AI arm had at least one

reported treatment emergent AE. In the abemaciclib + AI arm, the most common AEs (any grade reported by≥30% of the patients) included diarrhea (82 % versus 32% with placebo + AI), neutropenia (44 % versus 2% with placebo + AI), fatigue (41% versus 34% with placebo + AI), nausea (41% versus 21% with placebo + AI), anemia (32 % versus 8% with placebo + AI), abdominal pain (31% versus 13% with placebo + AI), and vomiting (30 % versus 13% with placebo + AI).[6] Grade 3 and 4 treatment emergent AEs were reported in 61.8% of abemaciclib-treated patients and 26.1% of placebo-treated patients.[6] SAEs were reported in 31.2% of patients in the abemaciclib + AI arm and 16.8% of those in the placebo + AI arm. Withdrawal rate due to AEs in the abemaciclib + AI arm (16.5%) was higher than that in the placebo + AI arm (3.1%). Death due to an AE was reported for eight patients (2.4%) receiving abemaciclib + AI and one patient (0.4%) receiving placebo + AI (Table 6.8).[6]

At the time of the 90-day safety update (11-Aug-2017), 135 patients in the abemaciclib + AI arm and 44 patients in the placebo + AI arm, continued to receive the assigned study treatments. The median duration of abemaciclib exposure was 66.57 weeks (range 20.00 to 104.43). The incidence of Grade 3 and 4 AEs was higher in the abemaciclib + AI arm, with 188 (57.7%) patients experiencing a Grade ≥3 event, as compared with 37 patients (23.0%) experiencing Grade ≥3 AEs in the placebo + AI arm. The most common Grade 3 or 4 AEs associated with abemaciclib + Ai was neutropenia 64 patients (21.1%). In the abemaciclib + AI arm, a total of 42 patients (12.8%) discontinued study treatment due to treatment emergent AEs versus four patients (2.5%) in the placebo plus AI arm. Dose reductions due to AEs occurred for 142 patients (43.4%) receiving abemaciclib + AI and 10 patients (6.2%) receiving placebo + AI. As o 11-Aug-2017, a total of 16 deaths were reported: 13 deaths with abemaciclib + AI and three with placebo + AI. Of these deaths, 10 deaths in the abemaciclib + AI arm and two deaths in the placebo + AI arm were attributed to AEs.[3]

At the 07-Nov-2017 data cut-off (final PFS analysis), a total of 323 patients (98.8%) in the abemaciclib + AI arm and 152 patients (94.4%) in the placebo + AI arm were reported with at least one AE. Diarrhea was the most common AE in the abemaciclib-treated patients (82.3% versus 32.3% in the placebo arm); however, most cases of diarrhea were reported to be of low grade (72.8% grade 1 or 2), with 69.1% of patients experiencing diarrhea in cycle 1. Neutropenia occurred in 43.7% of abemaciclib-treated patients (23.9% with grade 3 or 4 neutropenia) compared with 1.9% in the placebo arm (1.2% with grade 3 or 4 neutropenia). The incidence of venous thromboembolic events was also higher in the abemaciclib arm (6.1% versus 0.6% in the placebo arm). Dose reductions due to AEs occurred for 152 patients (46.5%) receiving abemaciclib + AI and 10 patients (6.2%) receiving placebo + AI. Overall, 25.1% of patients in the abemaciclib + AI arm and 4.3% of those in the placebo + AI arm discontinued any study drug due to an AE. A total of 18 deaths were reported: 15 deaths with abemaciclib + AI (11 due to AEs) and three (1.9%) with placebo + AI (two due to AEs). Three of the 15 deaths in the abemaciclib arm occurred after the interim analysis cut-off due to lung infection (n = 1), respiratory failure (n = 1), and a cerebrovascular accident (n = 1).[4]

Table 6.8: Summary of safety outcomes in the MONARCH 3 trial (Endocrine-Naïve/Sensitive)

	Number (%) of Patients	
Number of Patients[a]	Abemaciclib + NSAI N=327	Placebo + NSAI N=161
Patients with ≥1 TEAE	323 (98.8)	152 (94.4)
Related to study treatment[b]	309 (94.5)	91 (56.5)
Patients with ≥1 CTCAE ≥Grade 3 TEAE	202 (61.8)	42 (26.1)
Related to study treatment[b]	168 (51.4)	11 (6.8)
Patients with ≥1 SAE	102 (31.2)	27 (16.8)
Related to study treatment[b]	41 (12.5)	4 (2.5)
Patients who discontinued study treatment due to an AE[c]	54 (16.5)	5 (3.1)
Related to study treatment[b]	39 (11.9)	0
Patients who discontinued study treatment due to an SAE[c]	21 (6.4)	5 (3.1)
Related to study treatment[b]	12 (3.7)	0
Patients who died due to an AE on study treatment[d]	8 (2.4)	2 (1.2)
Related to study treatment[b]	4 (1.2)	0
Patients who died due to an AE within 30 days of discontinuation from study treatment[d]	3 (0.9)	0
Related to study treatment[b]	1 (0.3)	0

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients in the safety population; NSAI = nonsteroidal aromatase inhibitor; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

a Patients may be counted in >1 category.

b Includes events that were considered related to study treatment as judged by the investigator.

c Patients who died on study treatment with primary cause as AE or SAE were also included as discontinuations.

d Deaths were also included as SAEs and discontinuations due to AEs.

Source: o_ae_overview_2_old.rtf.

Source: EMA Public Assessment Report (EMA/551438/2018), page 100/133[6]

Data cut-off date: 31-Jan-2017

Table 6.9: Summary of adverse events reported in the MONARCH 3 trial

	Abemaciclib + NSAI N=327					Placebo + NSAI N=161				
	CTCAE Grade									
Preferred Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**All**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**All**
Patients with ≥1 TEAE, n (%)	19 (5.8)	102 (31.2)	169 (51.7)	22 (6.7)	323 (98.8)	40 (24.8)	70 (43.5)	36 (22.4)	4 (2.5)	152 (94.4)
Diarrhea	139 (42.5)	99 (30.3)	31 (9.5)	0	269 (82.3)	36 (22.4)	14 (8.7)	2 (1.2)	0	52 (32.3)
Neutropenia	12 (3.7)	53 (16.2)	72 (22.0)	6 (1.8)	143 (43.7)	0	1 (0.6)	1 (0.6)	1 (0.6)	3 (1.9)
Fatigue	70 (21.4)	59 (18.0)	6 (1.8)	NA	135 (41.3)	33 (20.5)	21 (13.0)	0	NA	54 (33.5)
Nausea	91 (27.8)	40 (12.2)	4 (1.2)	NA	135 (41.3)	30 (18.6)	1 (0.6)	2 (1.2)	NA	33 (20.5)
Anemia	31 (9.5)	49 (15.0)	23 (7.0)	0	103 (31.5)	8 (5.0)	3 (1.9)	2 (1.2)	0	13 (8.1)
Abdominal pain	72 (22.0)	24 (7.3)	6 (1.8)	NA	102 (31.2)	13 (8.1)	6 (3.7)	2 (1.2)	NA	21 (13.0)
Vomiting	66 (20.2)	28 (8.6)	5 (1.5)	0	99 (30.3)	15 (9.3)	2 (1.92)	4 (2.5)	0	21 (13.0)
Alopecia	83 (25.4)	7 (2.1)	NA	NA	90 (27.5)	18 (11.2)	0	NA	NA	18 (11.2)
Decreased appetite	51 (15.6)	30 (9.2)	5 (1.5)	0	86 (26.3)	13 (8.1)	3 (1.9)	1 (0.6)	0	17 (10.6)
Leukopenia	13 (4.0)	31 (9.5)	27 (8.3)	1 (0.3)	72 (22.0)	2 (1.2)	1 (0.6)	0	1 (0.6)	4 (2.5)
Blood creatinine increased	35 (10.7)	25 (7.6)	6 (1.8)	1 (0.3)	67 (20.5)	6 (3.7)	1 (0.6)	0	0	7 (4.3)
Headache	51 (15.6)	11 (3.4)	3 (0.9)	NA	65 (19.9)	20 (12.4)	6 (3.7)	0	NA	26 (16.1)
ALT increased	20 (6.1)	16 (4.9)	20 (6.1)	1 (0.3)	57 (17.4)	6 (3.7)	3 (1.9)	3 (1.9)	0	12 (7.5)
Arthralgia	43 (13.1)	14 (4.3)	0	NA	57 (17.4)	26 (16.1)	7 (4.3)	0	NA	33 (20.5)
Constipation	43 (13.1)	12 (3.7)	2 (0.6)	0	57 (17.4)	18 (11.2)	5 (3.1)	0	0	23 (14.3)
AST increased	28 (8.6)	15 (4.6)	12 (3.7)	0	55 (16.8)	8 (5.0)	2 (1.2)	2 (1.2)	0	12 (7.5)
Back pain	31 (9.5)	18 (5.5)	3 (0.9)	NA	52 (15.9)	15 (9.3)	10 (6.2)	1 (0.6)	NA	26 (16.1)
Rash	36 (11.0)	11 (3.4)	3 (0.9)	0	50 (15.3)	6 (3.7)	2 (1.2)	0	0	8 (5.0)
Cough	36 (11.0)	12 (3.7)	0	NA	48 (14.7)	16 (9.9)	4 (2.5)	0	NA	20 (12.4)
Pruritus	37 (11.3)	10 (301)	0	NA	47 (14.4)	14 (8.7)	1 (0.6)	0	NA	15 (9.3)
Dizziness	35 (10.7)	8 (2.4)	1 (0.3)	NA	44 (13.5)	15 (9.3)	3 (1.9)	0	NA	18 (11.2)
Stomatitis	34 (10.4)	7 (2.1)	0	0	41 (12.5)	12 (7.5)	5 (3.1)	0	0	17 (10.6)

Continued

	Abemaciclib + NSAI N=327					Placebo + NSAI N=161				
	CTCAE Grade									
Preferred Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**All**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**All**
Thrombocytopenia	24 (7.3)	7 (2.1)	8 (2.4)	2 (0.6)	41 (12.5)	2 (1.2)	2 (1.2)	1 (0.6)	0	5 (3.1)
Dyspnea	27 (8.3)	10 (3.1)	2 (0.6)	1 (0.3)	40 (12.2)	5 (3.1)	5 (3.1)	1 (0.6)	0	11 (6.8)
Influenza-like illness	29 (8.9)	10 (3.1)	0	0	39 (11.9)	10 (6.2)	5 (3.1)	0	0	15 (9.3)
Urinary tract infection	0	30 (9.2)	6 (1.8)	0	36 (11.0)	0	16 (9.9)	1 (0.6)	0	17 (10.6)
Weight decreased	20 (6.1)	13 (4.0)	3 (0.9)	NA	36 (11.0)	2 (1.2)	2 (1.2)	1 (0.6)	NA	5 (3.1)
Neuropathy	29 (8.9)	5 (1.5)	1 (0.3)	0	35 (10.7)	15 (9.3)	1 (0.6)	0	0	16 (9.9)
Pain in extremity	23 (7.0)	10 (3.1)	2 (0.6)	NA	35 (10.7)	11 (6.8)	8 (5.0)	0	NA	19 (11.8)
Bone pain	21 (6.4)	13 (4.0)	0	0	34 (10.4)	7 (4.3)	7 (4.3)	0	0	14 (8.7)
Myalgia	29 (8.9)	5 (1.5)	0	0	34 (10.4)	9 (5.6)	3 (1.9)	0	0	12 (7.5)
Pyrexia	30 (9.2)	3 (0.9)	1 (0.3)	0	34 (10.4)	13 (8.1)	4 (2.5)	0	0	17 (10.6)
Hot flush	26 (8.0)	7 (2.1)	0	NA	33 (10.1)	24 (14.9)	4 (2.5)	0	NA	28 (17.4)
Edema peripheral	26 (8.0)	7 (2.1)	0	0	33 (10.1)	9 (5.6)	1 (0.6)	0	0	10 (6.2)
Upper respiratory tract infection	1 (0.3)	32 (9.8)	0	0	33 (10.1)	0	9 (5.6)	0	0	9 (5.6)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients in the safety population; n = number of patients within category; NA = not applicable per CTCAE; NSAI = nonsteroidal aromatase inhibitor; TEAE = treatment-emergent adverse event.

Source: ae_pt_345.rtf.

Source: EMA Public Assessment Report (EMA/551438/2018), page 101/133[6]

Data cut-off: 31-Jan-2017

6.3 B) Results for Endocrine-Resistant HR+ HER2- advanced or metastatic breast cancer

6.3.1 B) Literature Search Results (Endocrine-Resistant)

See section 6.3.1A for literature search results.

6.3.2 B) Summary of Included Studies (Endocrine-Resistant)

6.3.2.1B)Detailed Trial Characteristics (Endocrine-Resistant)

One phase III randomized placebo-controlled trial evaluating the effects of abemaciclib in combination with fulvestrant in women with disease progression following endocrine therapy was identified. Characteristics of the MONARCH 2 trial are summarized in Table 6.10.

Table 6.10: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: MONARCH 2[7,10] NCT02107703[8] Characteristics : global randomized (2:1 ratio), double-blind, placebo-controlled, phase III N randomized: 446 (abemaciclib), 223 (placebo) N treated (≥1 dose): 441 (abemaciclib), 223(placebo) Number of centres and number of countries: 145 centres in 19 countries Patient Enrolment Dates: 07-Aug-2014 to 29-Dec-2015 Data cut-off: 14-Feb-2017 Final Analysis: to be performed after 441 OS events Funding: Eli Lilly	Key Inclusion Criteria: • ≥ 18 years of age • Female, any menopausal status • HR+, HER2- advanced or metastatic breast cancer • ECOG performance status ≤ 1. • measurable disease (by RECIST v1.1) or non-measurable bone-only disease • progressed while receiving prior endocrine therapy for advance breast cancer Key Exclusion Criteria: • prior treatment with fulvestrant, everolimus, or CDK 4, 6 inhibitors • presence of visceral crisis • evidence or history of CNS metastasis	Intervention: ‡ abemaciclib 150 mg orally twice daily on Days 1 to 28 (28-day cycles) + fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and Day 1 of subsequent cycles. Comparator: ‡ placebo orally twice daily on Days 1 to 28 (28-day cycles) + fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and Day 1 of subsequent cycles.	Primary: • PFS (Investigator-assessed) Secondary: Efficacy • ORR (CR, PR) • DoR • CBR • OS Safety • AEs • SAEs • WDAEs Other: • PROs /HrQoL • Bioanalytical • Pharmacokinetic • Pharmacodynamics

AE = adverse event; **CBR** = clinical benefit rate; **CNS** = central nervous system; **CR** = complete response; **DoR** = duration of response; **ECOG** = Eastern Cooperative Oncology Group; **HER2-** = human epidermal growth factor receptor 2-negative ; **HR+** = hormone receptor positive; **HrQoL** = health-related quality of life; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **PR** = partial response; **PROs** = patient-reported outcomes; **RECIST** = Response Evaluation Criteria in Solid Tumors; **SAE**= serious adverse event; **WDAE** = withdrawal due to adverse events

† The starting dose of blinded study drug (abemaciclib/placebo) was 200 mg twice daily. After a review of safety data the study was amended to reduce the dose of the study treatment to 150 mg twice daily for all (new and ongoing) patients.

‡ Pre- or peri-menopausal women received a gonadotropin-releasing hormone agonist.

Table 6.11: Select quality characteristics of included studies of abemaciclib in women with HR+ HER2- advanced breast cancer (Endocrine-Resistant)

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
MONARCH 2	Abemaciclib + fulvestrant vs placebo + fulvestrant	PFS (investigator-assessed)	630	669	Stratified randomization (2:1 ratio) interactive Web response system	Yes interactive Web response system	Yes Placebo-controlled	Yes	No	No	Yes

a) Trials (Endocrine-Resistant)

Trial design

MONARCH 2 was a phase III, multi-centre, randomized, double-blind, placebo-controlled study of fulvestrant with or without abemaciclib in women with HR+/HER2− advanced or metastatic breast cancer whose disease had progressed on previous endocrine therapy. The study was conducted in 142 centres in 19 countries.[7,8]

Eligible patients were randomized in a 2:1 ratio to receive abemaciclib + fulvestrant or placebo + fulvestrant (28-day cycles). All pre- or peri-menopausal women were also treated with a gonadotropin-releasing hormone agonist such as goserelin which was initiated 28 days prior to cycle 1, day 1.[9]

Notes:

- The study enrollment started on 07-Aug-2014.
- The starting dose of blinded study drug (abemaciclib/placebo) was 200 mg twice daily for a 28 day cycle. After a review of safety, the study was modified (amendment A) to reduce the dose of the study treatment to 150 mg twice daily for all (new and ongoing) patients.
- The initial study design included patients with or without prior endocrine therapy in the advanced or metastatic setting. However, the study was amended on 30-March-2015 (Amendment b) to exclude 44 randomized endocrine-naïve patients. These patients were not included by the investigators in the intent-to-treat (ITT) analyses. The ITT population included endocrine therapy pre-treated (endocrine-resistant) patients, defined as patients who had disease progression ≤12 months of completing adjuvant endocrine therapy or those who had progressed on or after first-line endocrine therapy for metastatic disease.[9] The request received from the Submitter for the reimbursement of abemaciclib + fulvestrant for HR+/HER2− advanced or metastatic breast cancer was consistent with the definition of the endocrine therapy resistant patients. Therefore, this pCODR review will focus on the effects of abemaciclib + fulvestrant in this patient population (i.e., endocrine-resistant).

More details about the trial design are provided below.

Randomization and treatment concealment

Randomization was performed using a centralized interactive web-based randomization system. Patients were randomized into abemaciclib + fulvestrant or placebo + fulvestrant arms in a 2:1 ratio. Randomization was stratified based on two factors:[7]

- nature of disease (visceral, bone only, or other); and
- endocrine therapy resistance (primary or secondary).

Prior to Protocol Amendment (b), randomization was also stratified by endocrine therapy naïve versus endocrine therapy pretreated. However, after this protocol amendment, all of the enrolled and randomized endocrine-naïve patients were removed from the ITT population.[9]

Primary endocrine therapy resistance was defined based on the European Society for Medical Oncology (ESMO) guidelines as: disease relapse within the first two years of neoadjuvant or adjuvant endocrine therapy, or disease progression within the first six months of endocrine therapy for advanced or metastatic breast cancer. Patients who were not considered to have primary endocrine therapy resistance were defined as having secondary resistance.[7]

Blinding of study participants and investigators was performed through the use of placebo capsules that matched abemaciclib capsules in size and color. Blinding codes could be broken in case of need for reasons of patient safety; or after a patient discontinued treatment due to disease progression, if deemed essential for the selection of the patient's next treatment regimen. The Lilly clinical research physician was required to be consulted prior to unblinding. If the investigator or patient became unblinded, the patient was to transition to post discontinuation follow up.[9]

Study endpoints and disease assessments

The primary endpoint of the study was investigator-assessed progression-free survival (PFS), defined as the time from randomization to disease progression (according to RECIST version 1.1) or death for any reason.[7,9]

Key secondary end points included:[7,9]

- Objective response rate (ORR) defined as the proportion of patients with a complete response (CR) or partial response (PR)
- Duration of response (DoR), defined as the time from CR or PR until disease progression or death
- Clinical benefit rate (CBR), defined as CR or PR or stable disease (SD) of ≥24 weeks duration
- Overall survival (OS), defined as the time from randomization to death from any cause
- Safety and tolerability

Other secondary end points included quality of life measures and pharmacokinetics. The trial also included the exploratory endpoint of change in tumor size.[9]

Tumour assessments were performed using computed tomography (CT) or magnetic resonance imaging (MRI) according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) within 28 days before random assignment (baseline) and then every 8 weeks during the first year, and every 12 weeks thereafter. In the presence of any evidence of clinical progression, imaging was to be performed within 14 days of clinical progression. Bone scintigraphy was conducted at

baseline, and then every 6th cycle starting with Cycle 7. Bioanalytical tests were performed centrally on Days 1 and 15 of Cycle 1, and Day 1 of all remaining cycles.[7,9]

Patient reported outcomes (PROs) measured using the Modified Brief Pain Inventory, Short Form (mBPI-sf), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and Breast Cancer (EORTC QLQ-BR23), and the EuroQol 5-Dimension 5-Level (EQ-5D-5L). PROs data were collected at baseline, Day 1 of Cycle 2, every second cycle beginning with Cycle 3 through Cycle 13, and then every third cycle after Cycle 13. Data were also collected at the short term follow up visit.[10]

Safety and tolerability of abemaciclib were assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Data on adverse events (AEs) were collected at the short term follow up visit (approximately 30 days after study therapy discontinuation). Serious AEs were evaluated due to long term follow-up, which began the day after short-term follow up is completed and continued until the study completion or patient's death. Survival assessments were performed every 12 weeks via telephone contact to the patient or their family during this period.[9]

Statistical analysis

Sample size calculation

The MONARCH 2 trial was initially planned to enroll 450 patients into the ITT population. However, after a change in the starting dose of the blinded-study drug from 200 mg to 150 mg, the sample size was increased to 630 patients to ensure at least 450 patients were enrolled at the 150-mg dose.[7] Details of sample size calculation are as follows:

The sample size calculation for the MONARCH 2 trial was event-driven. A total of 378 PFS events would be required for the final PFS analysis to provide approximately 90%power, assuming a hazard ratio (HR) of 0.703 at a one-sided α of 0.025. This HR corresponds to a 2.75-month improvement (42%) for the abemaciclib + fulvestrant arm over the true median PFS for the control arm which was assumed to be 6.5 months. One efficacy interim analysis was planned to be at 70%of the final PFS events (i.e., after 265 PFS events). To control the type I error rate at a one sided p of 0.025, the p-value of 0.00001 was specified for the interim PFS analysis, with the remaining α to be spent in the final PFS analysis.[7,9]

The final OS analysis was planned to be performed after approximately 441 OS events.[9] Type I error for the analysis of OS (secondary endpoint) was maintained using a hierarchical testing approach. The alpha-spending between the respective OS analyses was determined by an O'Brien-Fleming type stopping boundary.[6,9]

Interim analysis of the efficacy data occurred on the 14-Feb-2017 data cut-off date.

Efficacy analyses

The primary analysis of investigator-assessed PFS was performed on the ITT population, which included all randomized patients regardless of starting dose (200 mg or 150 mg of abemaciclib/placebo twice daily). However, sensitivity analysis were conducted to limit the analysis to patients who were enrolled after the change in starting dose and those with determined progression on the basis of a blinded, independent central review.[7] PFS was using a stratified log-rank test (stratified by metastatic site and endocrine therapy resistance). The odds ratio estimator and the stratified Cochran-Mantel-Haenszel test were used to compare the rates of binary end points. Two-sided P values were used to compare efficacy between treatment groups and for interaction tests associated with the subgroup factors. An exploratory mixed-model analysis was used to compare change in tumor size over time. Unless otherwise stated, all

hypothesis tests were performed at the two-sided 0.05 statistical significance level, and all confidence intervals were estimated at a 95% confidence level.[7]

Safety analysis

Safety was assessed in all patients who received at least one dose of study drug (i.e., the safety population). Safety and tolerability of abemaciclib was graded using the National CTCAE (version 4.03) and the results were reported descriptively. Additional safety analyses were conducted based on the dose reduction of abemaciclib from 200 mg twice daily to 150 mg twice daily.[6]

Patient-reported outcomes analyses

Patient reported outcomes (PROs) were collected for the MONARCH 2 study using the Modified Brief Pain Inventory, Short Form (mBPI-sf), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and Breast Cancer (EORTC QLQ-BR23), and the EQ-5D-5L. PROs were collected at baseline, cycle 2; then every two cycles from cycle3 through cycle 13; and every third cycle thereafter, during the treatment period and at the short term follow up.[9,10]

The primary health reported outcome was time-to-worsening of pain as measured by the mBPI-sf. Time-to-worsening of pain was defined based on a two-point increase in "worst-pain" score of the mBPI-sf or a one point increase in analgesic drug use. Analgesic drug use was classified into three categories: nonopioid, weak opioid, and strong opioid (one-point increase = moving to a stronger category).

Clinically meaningful differences from the baseline in EORTC scales were defined as ≥10 points change on a 0-100 scale. The statistical significance was set at $\alpha \leq 0.05$, with no adjustments for multiple comparisons.[10]

Note: no peer-reviewed publications reporting on the quality of life data from the MONARCH 2 trial were identified in this pCODR review. Data presented in this pCODR report was taken from a conference abstract and its related poster presentation that was provided by the Submitter.[10]

Protocol amendments

The first draft of the MONARCH 2 study protocol was issued in 01-Apr-2014. The protocol was amended four times:[9]

- Amendment (a)[12-Jan-2015]: modified the starting dose of study drug from abemaciclib (or placebo) 200 mg twice daily to 150 mg twice daily. Based on this amendment, patients who were receiving 200 mg twice daily were required to have a dose reduction to 150 mg every twice daily. At the time of the protocol amendment, there were 178 patients enrolled in the study; of whom, 121 patients were randomized to the abemaciclib arm. Of the patients 121v patient sin the abemaciclib arm, 56.2% had had a dose reduction due to AEs and 24% had discontinued treatment.
- Amendment (b) [30-Mar-2015]: removed the inclusion of endocrine therapy naïve patients, increased the sample size for endocrine therapy pre-treated patients, and updated the statistical analysis plan to include interim analyses. Endocrine therapy pretreated patients were defined as those who had disease progression ≤12 months of completing adjuvant endocrine therapy or patients who had progressed on or after first-line endocrine therapy for metastatic disease. Previously included endocrine therapy naïve patients (n=44) were excluded from the primary ITT analysis.
- Amendment (c) [27-Oct-2015]: updated guidance for dose adjustments in the setting of hematologic toxicity and diarrhea as well as guidance for the use of blood cell growth factors. The amendment also modified the statistical stopping boundary for the first interim analysis of efficacy corresponding to an HR of <0.56.

- Amendment (d) [29-Apr-2016]: removed the second planned interim analysis of efficacy and changed the primary efficacy analysis to occur earlier, given Phase III study results of fulvestrant in combination with another CDK 4/6 inhibitor.

b) Populations (Endocrine-Resistant)

Eligibility criteria:[6,7,9]

Eligible patients were women aged ≥18 years of any menopausal status (pre-, peri, or post-menopausal) who met the following key inclusion criteria:

- Locoregional or metastatic breast cancer not amenable to curative surgery
- ECOG performance score ≤ 1
- Estrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive tumor by immunohistochemistry (IHC) according to ASCO guidelines
- HER2-negative tumor by IHC or in-situ hybridization according to ASCO guidelines
- Measurable disease by RECIST (version 1.1), or non-measurable bone-only disease (i.e., blastic, lytic, or mixed)
- Relapse/progression while receiving or within 1 year of completing (neo) adjuvant endocrine therapy, no subsequent endocrine therapy OR relapse after 1st line metastatic treatment with an anti-estrogen or AI, no chemotherapy in the metastatic setting.
- Postmenopausal status due to either surgical/natural menopause or ovarian suppression (pre/perimenopausal) (initiated at least 28 days prior to Cycle 1, Day 1) with a gonadotropin releasing hormone (GnRH) agonist such as goserelin. Postmenopausal status due to surgical/natural menopause required ≥1 of the following criteria:
    - Prior bilateral oophorectomy
    - Age ≥60 years
    - Age <60 and amenorrheic for at least 12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle stimulating hormone (FSH) and estradiol levels in the postmenopausal range
- Adequate organ function based on protocol-defined criteria

Patients were excluded from the study if they had at least one of the following criteria:

- History of more than one previous endocrine therapy for advanced or metastatic breast cancer.
- Presence of visceral crisis or lymphangitic spread, evidence or history of CNS metastasis, inflammatory breast cancer
- A history of any other cancer except for non-melanoma skin cancer or carcinoma in situ of the cervix unless in complete remission with no therapy for a minimum of 3 years.
- Previous non- (neo) adjuvant chemotherapy, fulvestrant, everolimus or CDK4/6 inhibitor, initiated bisphosphonates or RANK-L targeted agent <7 days prior to randomization.
- A history of a major surgery within 14 days prior to randomization
- History of autologous or allogeneic stem cell transplant

Characteristics of the study population:[6,7,9]

A total of 669 endocrine-resistant patients (713 patients with the 44 excluded endocrine-naïve patients) were included in the MONARCH 2 trial, with 446 patients in the abemaciclib + fulvestrant arm and 223 in the placebo + fulvestrant arm.

Baseline demographic and disease characteristics of the ITT population are presented in Table 6.12.As shown, the baseline demographic and disease characteristics were well balanced between the study arms. All 669 enrolled patients were female, with the median age of 60 years (range 32 to 91). The majority of patients were Caucasian (53.1% , and 61.0% in the abemaciclib and placebo arms, respectively) or Asian (33.4% , and 29.1% in the abemaciclib and placebo arms, respectively); in a post-menopausal status (83.2% , and 80.7% in the abemaciclib and placebo arms, respectively); and had a measurable disease (71.3% , and 73.5% in the abemaciclib and placebo arms, respectively). Prior treatments were also well-balanced between the two study arms. Approximately 60% of the patients in each arm had received a prior adjuvant or neoadjuvant chemotherapy. At the baseline, 70.9% of patients in the abemaciclib + fulvestrant arm and 66.8% of those in the placebo + fulvestrant arm had received a prior AI.

Table 6.12: Patient and disease characteristics of the study population in the MONARCH 2 trial

Table 1. Patient and Disease Baseline Characteristics

Characteristic	Abemaciclib + Fulvestrant (n = 446)	Placebo + Fulvestrant (n = 223)
Age, years, median (range)	59 (32-91)	62 (32-87)
ET resistance*		
Primary	111 (24.9)	58 (26.0)
Secondary	326 (73.1)	163 (73.1)
Most recent ET†		
Neoadjuvant or adjuvant	263 (59.0)	133 (59.6)
Metastatic	171 (38.3)	85 (38.1)
Prior AI		
Yes	316 (70.9)	149 (66.8)
No	130 (29.1)	74 (33.2)
PgR status‡		
Positive	339 (76.0)	171 (76.7)
Negative	96 (21.5)	44 (19.7)
Metastatic site§		
Visceral	245 (54.9)	128 (57.4)
Bone only	123 (27.6)	57 (25.6)
Other	75 (16.8)	38 (17.0)
Measurable disease		
Yes	318 (71.3)	164 (73.5)
No	128 (28.7)	59 (26.5)
Race‖		
Asian	149 (33.4)	65 (29.1)
Caucasian	237 (53.1)	136 (61.0)
Other	29 (6.5)	13 (5.8)
ECOG performance status¶		
0	264 (59.2)	136 (61.0)
1	176 (39.5)	87 (39.0)
Prior chemotherapy for neoadjuvant or adjuvant treatment		
Yes	267 (59.9)	134 (60.1)
No	179 (40.1)	89 (39.9)
Menopausal status#		
Pre- or perimenopause	72 (16.1)	42 (18.8)
Postmenopause	371 (83.2)	180 (80.7)

Note. Data given as No. (%) unless otherwise indicated.
Abbreviations: AI, aromatase inhibitor; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; PgR, progesterone receptor.
*Six patients in the abemaciclib arm and two patients in the placebo arm had not received prior ETs.
†ET history was not available for 12 patients in the abemaciclib arm and five patients in the placebo arm.
‡Eight patients in each arm had unknown PgR status.
§Metastatic site was not available for three patients in the abemaciclib arm.
‖A total of 31 patients in the abemaciclib arm and nine in the placebo arm had missing race information.
¶One patient had ECOG performance status of 2 in the abemaciclib arm.
#Menopausal status was not available for three patients in the abemaciclib arm and one in the placebo arm.

Sledge, G.W. Jr. et al: J Clin Oncol. 35(25):2875-2884.[7]

c) Interventions (Endocrine-Resistant)

Treatment Dosing Schedule[6,7,9]

Patients were randomized to the following two treatment arms:

- Patients in the abemaciclib + fulvestrant arm received abemaciclib 150 mg orally twice daily [200 mg twice daily prior to the protocol amendment (a)] on Days 1 to 28 of a 28-day cycle plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond.
- Patients in the placebo + fulvestrant arm received placebo orally twice daily on Days 1 to 28 of a 28-day cycle plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond.

Pre- and peri-menopausal women (17% of the ITT population) received a GnRH agonist such as goserelin starting at least 28 days prior to study initiation and continued receiving concurrent ovarian function suppression with goserelin administered every 28 days during the active treatment phase.

Patients continued to receive assigned treatment until disease progression, death, or patient withdrawal. Patients in the abemaciclib + fulvestrant arm received a median of 15 cycles compared with nine cycles in the placebo + fulvestrant arm. Patients who received 200 mg of abemaciclib before the protocol amendment (a) (n = 121; 27.4%) received a median of 34 days of drug before dose reduction or discontinuation.

Crossover between treatment arms was not allowed. However, if drug-related toxicities mandated discontinuation of either abemaciclib or placebo, patients could continue to receive fulvestrant alone. Similarly, if fulvestrant required discontinuation, patients were permitted to continue receiving abemaciclib or placebo.

Dose modifications and interruptions[6,7,9]

For patients who reported significant treatment-related toxicities, dose modifications (interruptions or reductions) were permitted for abemaciclib or placebo according to pre-specified dose-adjustment procedures. There were two recommended dose adjustment schedules (150 mg to 100mg and 100mg to 50mg, all administered twice daily). Fulvestrant dose reductions were also permitted per US label as determined by the investigator. As mentioned earlier in this section, when treatment interruption was deemed necessary for one of the study drugs in the combination, treatment with the other drug could be continued.

The abemaciclib dose was reduced due to AEs in 189 patients (42.9%) compared with three (1.3%) receiving placebo.in addition, abemaciclib was interrupted due to AEs in 229 patients (51.9%) and in 26 patients (11.7%) in the placebo arm.

For patients requiring dose reductions, re-escalation to a previous dose was permitted only after consultation with a Lilly clinical research physician.

Concomitant and subsequent interventions[6,9]

The most common concomitant medications during the course of the study included antidiarrheals (75.5% with abemaciclib versus 17.9% with placebo), analgesics 66.2% with abemaciclib versus 62.3% with placebo, and bone modifying agents 45.6% with abemaciclib versus 49.8% with placebo.[6]

Table 6.13 summarizes the subsequent treatment patients received after discontinuation of abemaciclib or placebo. A larger proportion of patients in the abemaciclib + fulvestrant arm received a surgical procedure.

Patients could receive surgery with or without radiotherapy if the tumour was operable after receiving the study therapy. In this case, the study treatment should be discontinued for at least 7 days prior to surgery and until at least 14 days after surgery (± radiotherapy) to allow for tissue healing and recovery. Palliative radiation was not permitted without permanent discontinuation from study treatment.

Table 6.13: subsequent (post-discontinuation) treatments in the MONARCH 2 trial

	Abemaciclib N=446 n (%)	Placebo N=223 n (%)	Total N=669 n (%)
Patients remaining on treatment	170 (38.1)	45 (20.2)	215 (32.1)
Patients off treatment as of 2/14/17	271 (60.8)	178 (79.8)	449 (67.1)
Systemic therapy			
Overall	200 (44.8)	141 (63.2)	341 (51.0)
Chemotherapy	138 (30.9)	97 (43.5)	235 (35.1)
Endocrine	110 (24.7)	77 (34.5)	187 (28.0)
Other	25 (5.6)	15 (6.7)	40 (6.0)
Targeted	65 (14.6)	54 (24.2)	119 (17.8)
First subsequent line			
Chemotherapy	109 (24.4)	74 (33.2)	183 (27.4)
Endocrine	89 (20.0)	66 (29.6)	155 (23.2)
Other	17 (3.8)	12 (5.4)	29 (4.3)
Targeted	51 (11.4)	39 (17.5)	90 (13.5)
Surgical procedure	14 (3.1)	3 (1.3)	17 (2.5)
Radiotherapy	37 (8.3)	26 (11.7)	63 (9.4)

Source: MONARCH 2 CSR page 119.

Source: FDA Multi-disciplinary Review and Evaluation (NDA 208716), Table 31, page 142[9]

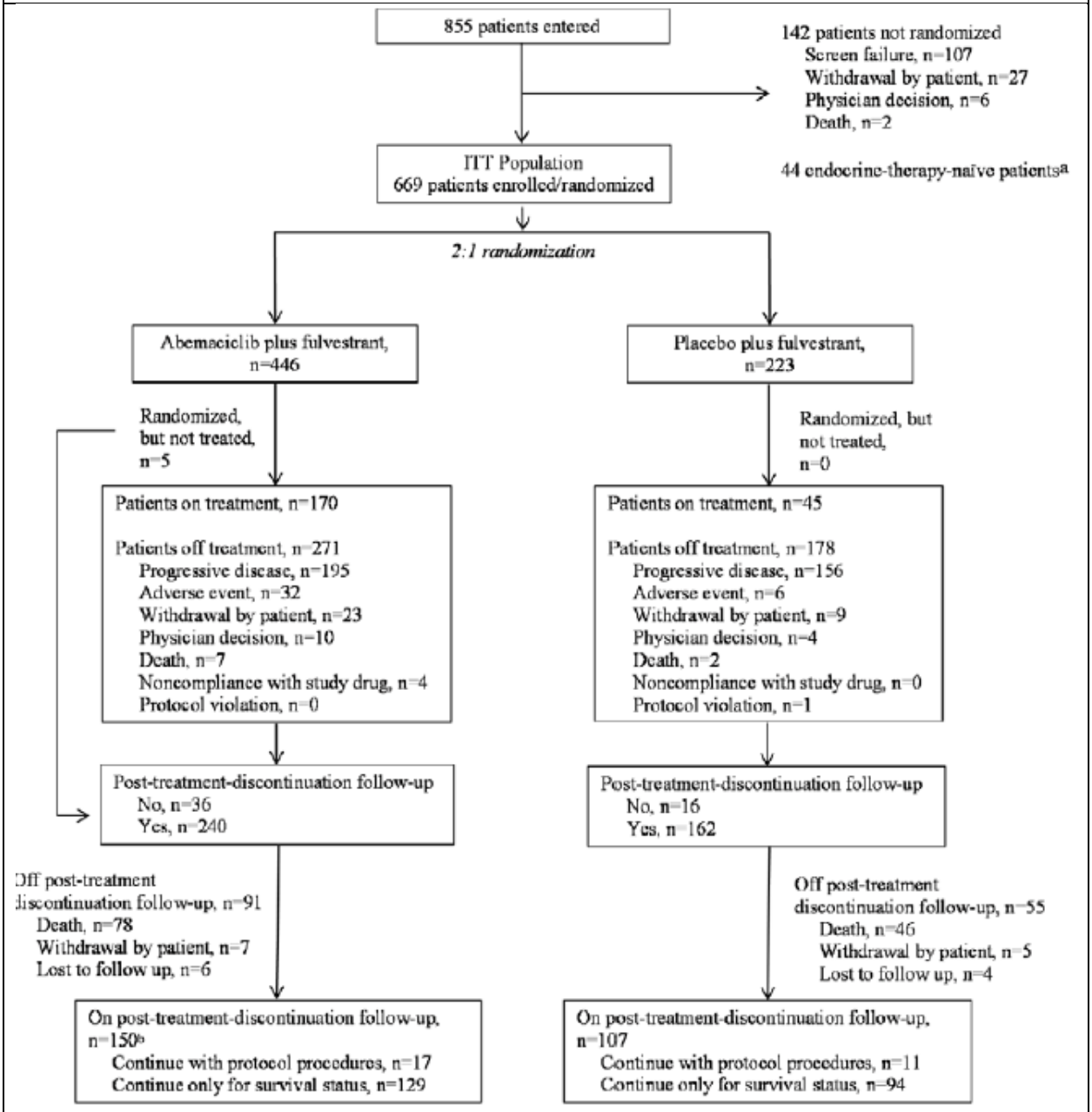
d) Patient Disposition (Endocrine-Resistant)[6,7,9]

From 07-Aug-2014, to 29-Dec-2015, a total of 669 endocrine resistant patients were randomized to receive abemaciclib + fulvestrant (n=446) or placebo + fulvestrant (n=223). Five patients randomized to abemaciclib did not receive the study treatment; and 441/446 patients in the abemaciclib + fulvestrant arm and all 223 patients in the placebo + fulvestrant arm received the study treatment.

At the 14-Feb-2017data cut-off date, 170 patients (38.1%) in the abemaciclib + fulvestrant arm and 45 (20.2%) patients in the placebo + fulvestrant arm were still on study treatment, while 271 patients (60.8%) in the abemaciclib + fulvestrant arm and 178 patients (79.8%) in the placebo + fulvestrant arm had discontinued the study treatment.

Figure 6.9 presents the patient disposition for the MONARCH 2 trial. As shown, the most common reasons for study-treatment discontinuation included disease progression, AEs, and patient withdrawal.

Figure 6.9: Patient disposition in the MONARCH 2 trial



Source: EMA Public Assessment Report (EMA/551438/2018), page 73/133[6]

Protocol violations/deviations

A total of 349 patients (80.5%) in the abemaciclib + fulvestrant arm and 181 patients (81.2%) in the placebo + fulvestrant arm had one or more major protocol deviations. The incidence of major protocol deviations in the MOARCH 2 trial are summarized in Table 6.14.

Table 6.14: Major protocol deviations in the MONARCH 2 trial

Deviation Category	Abemaciclib N=446 n (%)	Placebo N=223 n (%)	Total N=669 n (%)
Patients with ≥1 major protocol deviation	359 (80.5)	181 (81.2)	540 (80.7)
Key measurements not collected properly	235 (52.7)	114 (51.1)	349 (52.2)
Incorrect stratification factors for IWRS	164 (36.8)	83 (37.2)	247 (36.9)
Inclusion/Exclusion criteria not met	73 (16.4)	38 (17.0)	111 (16.6)
Improper treatment discontinuation	46 (10.3)	37 (16.6)	83 (12.4)
Improper administration of informed consent	55 (12.3)	21 (9.4)	76 (11.4)
Incorrect dose adjustments	33 (7.4)	9 (4.0)	42 (6.3)
Inappropriate handling of the investigational product	24 (5.4)	12 (5.4)	36 (5.4)
Other	12 (2.7)	5 (2.2)	17 (2.5)
Use of prohibited concomitant medications	2 (0.4)	2 (0.9)	4 (0.6)

Source MONARCH 2 CSR, page 85 with additional review of Table JPBL.14.2

Source: FDA Multi-disciplinary Review and Evaluation (NDA 208716), Table 23 page 134[9]

e) Limitations/Sources of Bias (Endocrine-Resistant)

Overall, MONARCH 2 trial was a well-designed RCT, with the following steps taken to minimize potential biases:

- A double-blind study design was employed to minimize bias in the assessment and reporting of all study outcomes; study participants and investigators were blinded to the treatment assignment. However, considering the high incidence of diarrhea in the abemaciclib + fulvestrant arm (see section 3.2.2.A for detailed safety outcome results) blinding would be difficult to maintain for both patients and investigators.
- To reduce selection bias, allocation concealment was performed through a centralized interactive web-based randomization system.
- A 2:1 randomization ratio was used to increase the probability that eligible patients that would be randomized to receive abemaciclib + fulvestrant, and to increase feasibility.
- A stratified randomization procedure based on two known prognostic factors (i.e., metastatic sites, type of resistance to endocrine therapy), was used to minimize potential imbalances between the study groups that might lead to biased results.
- Blinded independent central review (BICR) of radiological scans to reduce detection bias.
- The study adjusted for multiplicity for the analysis of key secondary outcome (i.e., OS). However, there was no formal analysis plan or alpha spending function for other secondary endpoints. Therefore, these analyses are considered descriptive.
- MONARCH 2 collected PRO data as an exploratory endpoint, using validated and reliable tools. The completion rates for all questionnaires were reported to be above 90% for most cycles.
- Sensitivity analyses were performed to investigate the influences of censoring and potential sources of bias.

The key limitations of the MONARCH 2 trial included:

- The absence of mature OS data at the time of interim analysis.
- After protocol amendment b (30-Mar-2015), MONARCH 2 excluded all endocrine therapy naïve patients from the ITT analysis, and focused the study objectives on evaluating treatment effects in endocrine-resistant patients. Therefore, the effects of abemaciclib + fulvestrant cannot be evaluated in this trial.

- Duration of therapy was longer in the experimental as compared to the control arm (13 months and 9 months respectively) with a median number of cycles of abemaciclib

received per patient of 13 as compared to 9 cycles in the control arm. Dose intensity was higher in the abemaciclib + fulvestrant arm (median 273 mg/day and mean 261 mg/day in the experimental arm versus median 298 mg/day and mean 309 mg/day in the placebo + fulvestrant arm).

- A relative high number of patients (>80%) had one or more major protocol deviations, with the "*key measurements not collected properly*" and "*incorrect stratification factors for IWRS*" being the most frequent types of protocol deviation. However, the deviations are well balanced and seem to be less likely to impact the study endpoints.

6.3.2.2B) Detailed Outcome Data and Summary of Outcomes (Endocrine-Resistant)

Efficacy Outcomes (Endocrine-Resistant)

Progression-Free Survival (PFS) *(Endocrine-Resistant)*

PFS (investigator-assessed) was the primary endpoint in the MONARCH 2 trial. The primary analysis of PFS data was conducted on 14-Feb-2017data cut-off date, when 379 progression events (disease progression or death) had occurred (378 events were planned for in the protocol). After a median follow-up duration of 19.5 months, a total of 222 patients (49.8%) in the abemaciclib + fulvestrant arm and 157 patients (70.4%)] in the placebo + fulvestrant arm had a PFS event.[7,9]

The median PFS was 16.4 months with abemaciclib + fulvestrant and 9.3 months with placebo + fulvestrant (HR = 0.553; 95% CI 0.449, 0.681; P < 0.001; Fig 6.10A). The primary analysis of investigator-assessed PFS demonstrated a statistically significant improvement in PFS with the addition of abemaciclib to fulvestrant. The results of the blinded central analysis was consistent with those of the primary analysis (HR = 0.460; 95% CI 0.363, 0.584; P < 0.001; Fig 6.10B).[7,9]

The sensitivity analysis that excluded patients who had received abemaciclib at 200mg twice daily dose prior to Amendment (a), yielded consistent results to the primary ITT analysis (HR = 0.588; 95% CI, 0.458 to 0.754).[7,9]

A summary of the subgroup analyses of PFS, by prognostic demographic and disease characteristics, are presented in Figure 6.11.[7] As shown, the PFS benefit maintained across the pre-defined patient subgroups.

Figure 6.10: Kaplan-Meier curves of progression-free survival in the MONARCH 2 trial

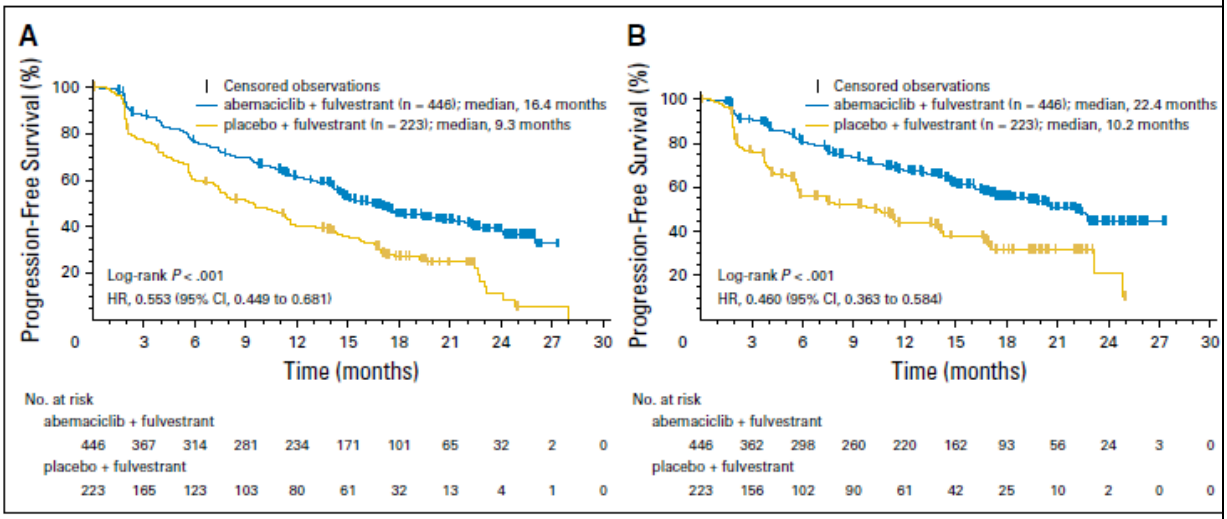
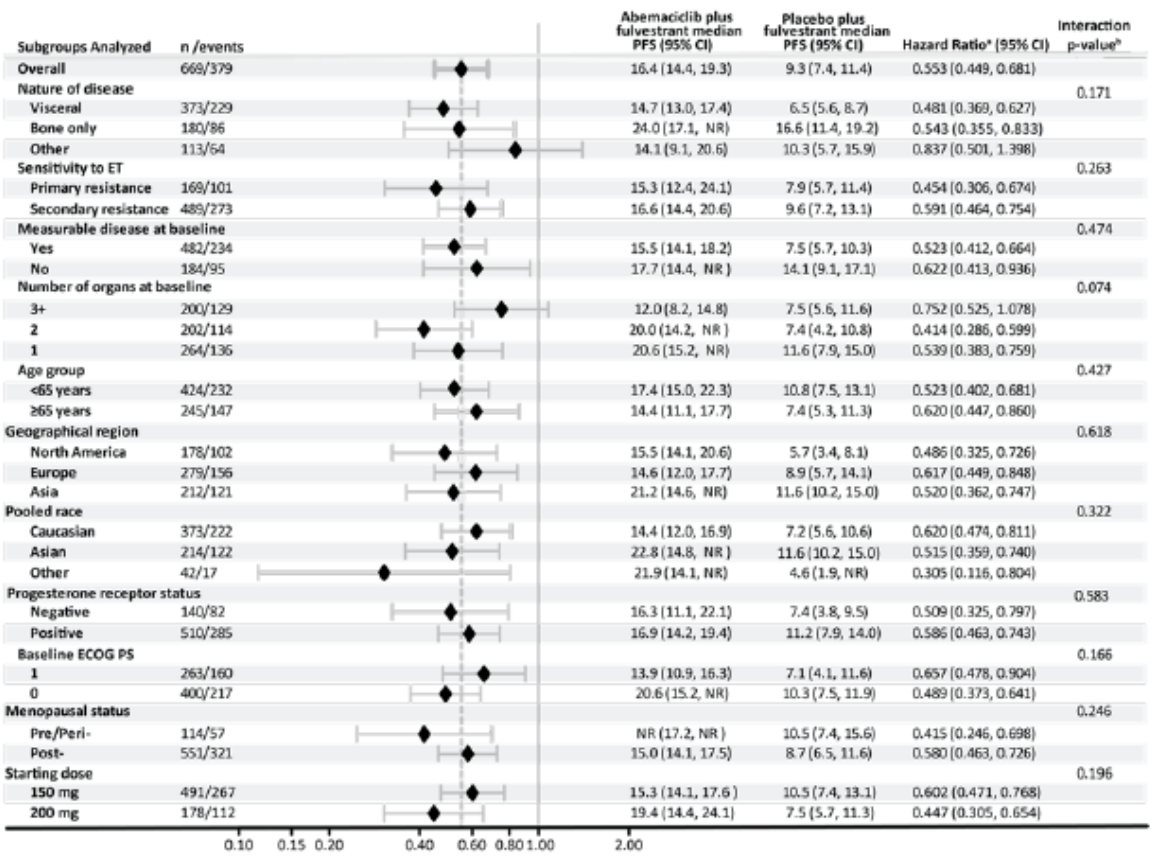


Fig 2. Kaplan-Meier plots of progression-free survival. (A) Investigator-assessed and (B) independent central review of intent-to-treat population. HR, hazard ratio.

Figure 6.11: Preplanned PFS subgroup analyses in the MONARCH 2 trial



Source: EMA Public Assessment Report (EMA/551438/2018); page 76/133[6]

Overall Survival (OS) *(Endocrine-Resistant)*

OS was a key secondary endpoint in the MONARCH 2 trial. At the 14-Feb-2017 data cut-off date, OS results were immature, with a total of 133 deaths (85 deaths [19.1%] in the abemaciclib + fulvestrant arm and 48 deaths [21.5%] in the placebo + fulvestrant arm). The median OS was not reached in neither of the arms. The results of the OS analysis are summarized in Table 6.15 and the Kaplan- Meier curves are presented in Figure 6.12).[7,9]

The final OS analysis is planned to be performed after occurrence of 441 death events.

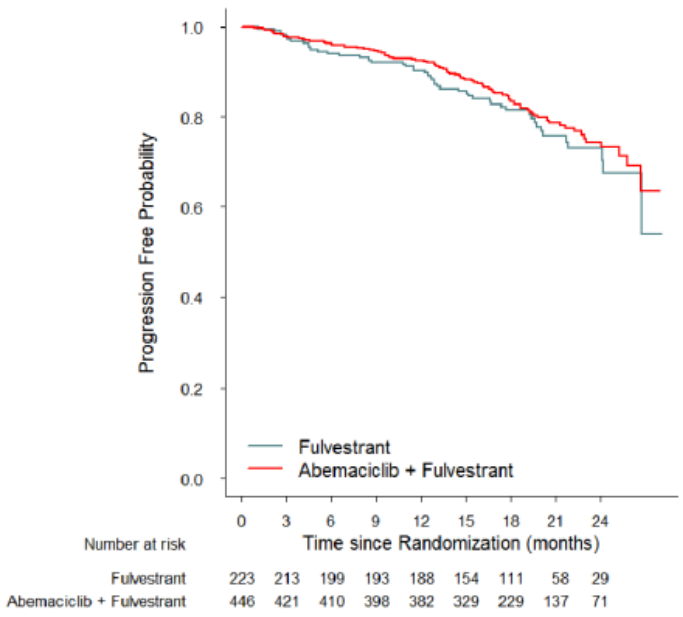
Table 6.15: Summary of OS Results from the MONARCH 2 trial

	Abemaciclib plus Fulvestrant N = 446	Placebo plus Fulvestrant N = 223
Deaths, n (%)	85 (19.1)	48 (21.5)
Censored, n (%)	361 (80.9)	175 (78.5)
Median, months (95% CI)	NE (26.7, NE)	NE (26.8, NE)
Hazard ratio, estimate (95% CI)	0.854 (0.598, 1.221)	
p-value	0.38	

Source: CSR Table JPBL.11.18. NE=not estimable

Source: FDA Multi-disciplinary Review and Evaluation (NDA 208716), Table 42 page 155[9]

Figure 6.12: Kaplan-Meier curves of overall survival in the MONARCH 2 trial



Source: FDA Multi-disciplinary Review and Evaluation (NDA 208716), Figure 9 page 156[9]

Objective Response Rate (ORR) *(Endocrine-Resistant)*

ORR was a secondary endpoint in the MONARCH 2 trial. As of the 14-Feb-2017 data cut-off date, after a median follow-up duration of 19.5 months, ORR was reported to be 35.2% (95% CI 30.8, 39.6) in the abemaciclib + fulvestrant arm and 16.1% (95% CI 11.3, 21.0) in the placebo + fulvestrant arm (p<0.001). Overall, 14 patients (3.1%) in the abemaciclib + fulvestrant arm and one patient (0.4%) in the placebo + fulvestrant arm achieved a CR.[7,9]

For patients with measurable disease, ORR was 48.1% (95% CI 42.6, 53.6) in the abemaciclib + fulvestrant arm versus 21.3% (95% CI 15.1, 27.6) in the placebo + fulvestrant arm (P < 0.001).[7,9]

Duration of Response (DOR) ***(Endocrine-Resistant)***

DOR was a secondary endpoint in the MONARCH 2 trial. At the data cut-off date, the median time to response was estimated to be 3.7 months (interquartile range [IQR] 1.7, 16.9) with abemaciclib + fulvestrant and 4.0 months (IQR 1.9, 14.7) with placebo + fulvestrant. The median DoR for patients in the abemaciclib + fulvestrant arm was not reached (95% CI, 18.05 months, not estimable), and 90 responders (57.3%) were continuing to receive treatment at the time of the primary analysis.[7,9]

Clinical Benefit Rate (CBR) ***(Endocrine-Resistant)***

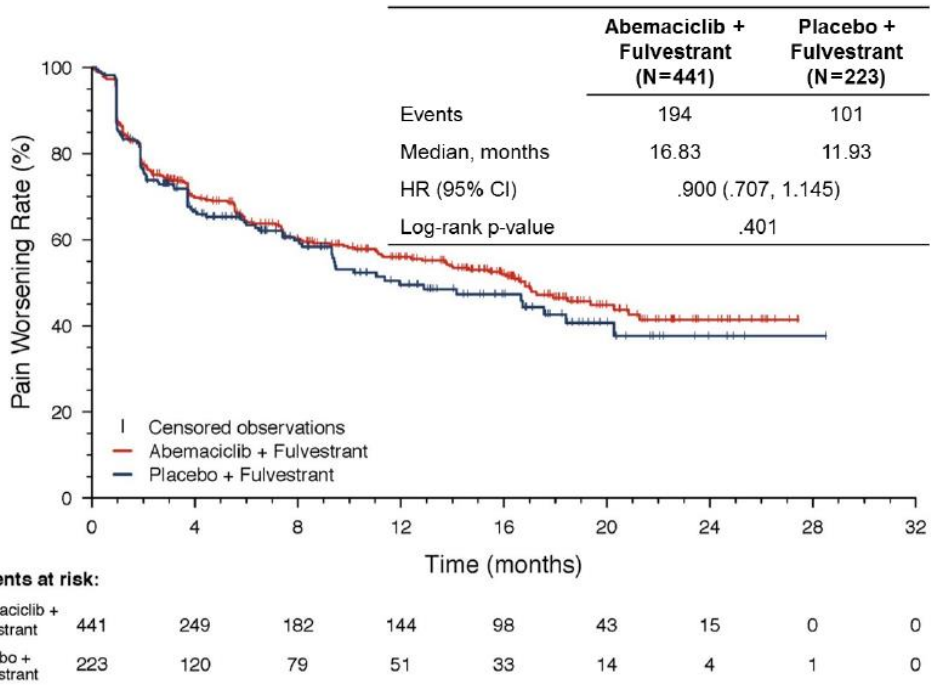
CBR was a secondary endpoint in the MONARCH 2 trial and was defined as response (CR or PR) or prolonged stable disease (≥6 months) according to the RECIST version 1.1.[9] At the 14-Feb-2017 data cut-off date, CBR was 72.2% (95% CI, 68.0% to 76.4%) in the abemaciclib + fulvestrant arm and 56.1% (95% CI, 49.5% to 62.6%) in the placebo + fulvestrant arm (P < 0.001). Best response of prolonged stable disease was lower in the abemaciclib + fulvestrant arm (9.0%) than that in the placebo + fulvestrant arm (20.2%).[7]

Quality of Life (Endocrine-Resistant)

The questionnaire completion rates for the EORTC QLQ-C30, EORTC QLQ-BR23, EQ 5D- 5L and mBPI-sf were reported to be above 90% for most cycles.[9]

The primary health reported outcome was time-to-progression of pain as measured by the mBPI-sf. A Kaplan- Meier plot of time-to-progression is shown in Figure 6.13. As shown, Treatment with abemacilib + fulvestrant delayed the median time to worsening of pain was by approximately five months (16.8 months in the abemaciclib arm versus 11.9 months in the palcebo arm) However, this difference was not statistically significant (HR= 0.900; 95% CI 0.707, 1.145; p=0.40).[10]

Figure 6.13: Time to pain worsening in the MONARCH 2 trial



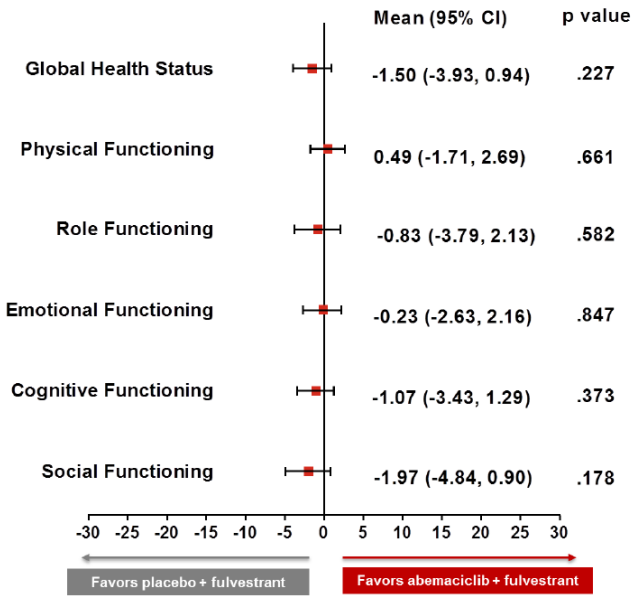
Source: Kaufman et al, ASCO 2018, Poster#1049 (in manufacturer submission), Figure 5[10]

As shown in Figure 6.14, changes from baseline in the following three EORTC QlQ-C30 were statistically different between the two study arms, all favoring the placebo arm: nausea and vomiting (mean change = 3.42; 95% CI 1.68, 5.15; p<0.001), appetite loss (mean change = 5.31; 95% CI 2.49, 8.13; p<0.001), and diarrhea (mean change = 24.64; 95% CI 21.58, 27.71; p<0.001). There was also a clinically meaningful (≥10 points) difference between the two groups in terms of change from the baseline in diarrhea score.[10]

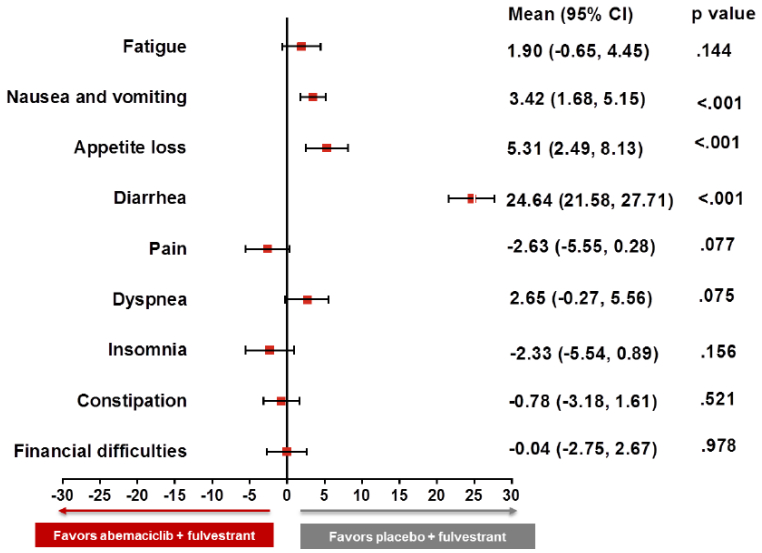
No statistically significant or clinically meaningful differences were observed between the two groups in terms of EORTC QlQ-BR23 functional scales, except for systemic therapy side effects (dry mouth, eye symptoms, hair loss, hot flashes, etc.) which were significantly worse in the abemaciclib + fulvestrant arm (mean change = 5.21; 95% CI 3.49, 6.92; p<0.001; Figure 6.15).[10]

Figure 6.14: Forest plots comparing mean change from baseline in EORTC QlQ-C30 functional and symptom scales

A. Functioning

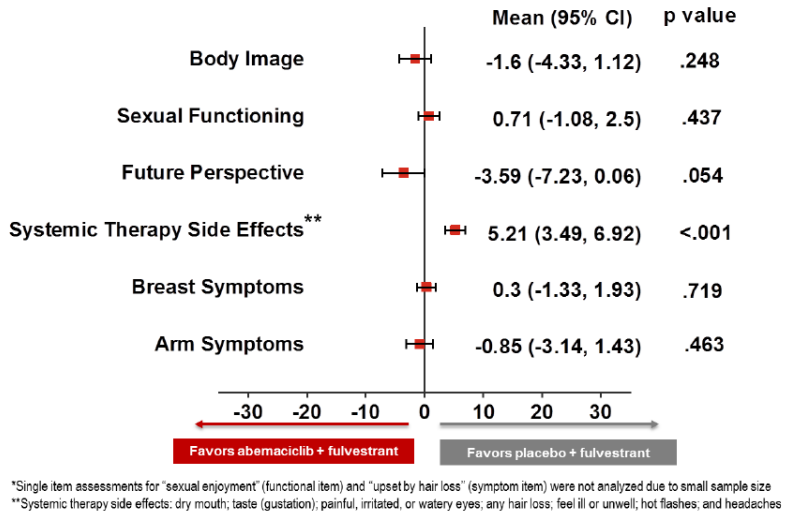


B. Symptoms



Source: Kaufman et al, ASCO 2018, Poster#1049 (in manufacturer submission), Figures 1A and 1B[10]

Figure 6.15: Forest plots comparing mean change from baseline in EORTC QlQ-BR23 functional and symptom scales



Source: Kaufman et al, ASCO 2018, Poster#1049 (in manufacturer submission), Figure 4[10]

Harms Outcomes (Endocrine-Resistant)

Of the 669 endocrine therapy resistant patients enrolled in the MONARCH 2 trial, a total of 664 patients were treated (441 patients in the abemaciclib + fulvestrant arm and 223 patients in the placebo + fulvestrant arm) and were included in the safety analysis. The safety analysis results are summarized in Table 6.16 and the types and frequencies of AEs are provided in Table 6.17.

As of the 14-Feb-2017 data cut-off date, after a median follow-up of 19.5 months, 98.6% of patients in the abemaciclib + fulvestrant arm and 89.2% of those in the placebo + fulvestrant arm had at least one reported treatment emergent AE. In the abemaciclib + fulvestrant arm, the most common AEs (any grade reported by≥10% of the patients) included diarrhea (86 % versus 35% with placebo + fulvestrant), neutropenia (46 % versus 4.0% with placebo + fulvestrant), nausea (45 % versus 23% with placebo + fulvestrant), fatigue (40% versus 27% with placebo + fulvestrant), abdominal pain (35 % versus 16% with placebo + fulvestrant), anemia (29 % versus 4% with placebo + fulvestrant), leukopenia (28 % versus 2% with placebo + fulvestrant), vomiting (26 % versus 10% with placebo + fulvestrant), headache (20 % versus 15% with placebo + fulvestrant), dysgausia (18% versus 3% with placebo + fulvestrant), and alopecia (16 % versus 2% with placebo + fulvestrant).[6] Grade 3 or 4 treatment-emergent AEs were reported for 62.6% of patients in the abemaciclib + fulvestrant arm and 23.8% of those in the placebo + fulvestrant arm), with the most frequent Grade≥ 3 AE with the abemaciclib combination being neutropenia (26.5% versus 1.8% in the placebo combination arm)(Table 6.16).[6]

SAEs were reported in 22.4% of patients in the abemaciclib + fulvestrant arm and 10.8% of those in the placebo + fulvestrant arm. Withdrawal rate due to AEs in the abemaciclib + fulvestrant arm (8.6%) was higher than the placebo + fulvestrant arm (3.1%).[6] Deaths due to AEs were reported in six patients (1.4 %) receiving abemaciclib + fulvestrant and one patient (0.4%) receiving placebo + fulvestrant (Table 6.17).[6]

Table 6.16: Summary of safety outcomes in the MONARCH 2 trial

Number of Patients[a]	Number (%) of Patients: Abemaciclib + Fulvestrant N=441	Number (%) of Patients: Placebo + Fulvestrant N=223
Patients with ≥1 TEAE	435 (98.6)	199 (89.2)
Related to study treatment[b]	420 (95.2)	134 (60.1)
Patients with ≥1 CTCAE ≥Grade 3 TEAE	276 (62.6)	53 (23.8)
Related to study treatment[b]	232 (52.6)	13 (5.8)
Patients with ≥1 SAE	99 (22.4)	24 (10.8)
Related to study treatment[b]	39 (8.8)	3 (1.3)
Patients who discontinued study treatment due to an AE[c]	38 (8.6)	7 (3.1)
Related to study treatment[b]	30 (6.8)	4 (1.8)
Patients who discontinued study treatment due to an SAE[c]	18 (4.1)	3 (1.3)
Related to study treatment[b]	12 (2.7)	0
Patients who died due to an AE on study treatment[d]	6 (1.4)	1 (0.4)
Related to study treatment[b]	4[d] (0.9)	0
Patients who died due to an AE within 30 days of discontinuation from study treatment[e]	3 (0.7)	1 (0.4)
Related to study treatment[b]	1 (0.2)	0

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients in the safety population; n = number of patients in the specified category; SAE = serious adverse events; TEAE = treatment-emergent adverse event.

a Patients may be counted in >1 category.

b Includes events that were considered related to study treatment (either abemaciclib/placebo or fulvestrant) as judged by the investigator.

c Patients who died on study treatment with primary cause as AE or SAE are also included as discontinuations.

d The death due to AE for Patient 1687 was not considered related by the investigator in the clinical database. However, in the information submitted to the Lilly Safety System database, the investigator indicated that this death was related to blinded study drug.

e Deaths are also included as SAEs and discontinuations due to AEs.

Data cut-off date: 14-Feb-2017

Source: EMA Public Assessment Report (EMA/551438/2018), page 107/133[6]

Table 6.17: Summary of adverse events reported in the MONARCH 2 trial

	Abemaciclib + Fulvestrant N=441					Placebo + Fulvestrant N=223				
	CTCAE Grade									
Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	All	Grade 1	Grade 2	Grade 3	Grade 4	All
Patients with ≥1 TEAE, n (%)	26 (5.9)	133 (30.2)	241 (54.6)	26 (5.9)	435 (98.6)	64 (28.7)	82 (36.8)	46 (20.6)	5 (2.2)	199 (89.2)
Diarrhea	182 (41.3)	140 (31.7)	59 (13.4)	0	381 (86.4)	43 (19.3)	11 (4.9)	1 (0.4)	0	55 (24.7)
Neutropenia	23 (5.2)	63 (14.3)	104 (23.6)	13 (2.9)	203 (46.0)	4 (1.8)	1 (0.4)	3 (1.3)	1 (0.4)	9 (4.0)
Nausea	129 (29.3)	58 (13.2)	12 (2.7)	NA	199 (45.1)	38 (17.0)	11 (4.9)	2 (0.9)	NA	51 (22.9)
Fatigue	100 (22.7)	64 (14.5)	12 (2.7)	NA	176 (39.9)	48 (21.5)	11 (4.9)	1 (0.4)	NA	60 (26.9)
Abdominal pain	103 (23.4)	42 (9.5)	11 (2.5)	NA	156 (35.4)	24 (10.8)	9 (4.0)	2 (0.9)	NA	35 (15.7)
Anemia	29 (6.6)	67 (15.2)	31 (7.0)	1 (0.2)	128 (29.0)	4 (1.8)	2 (0.9)	2 (0.9)	0	8 (3.6)
Leukopenia	24 (5.4)	62 (14.1)	38 (8.6)	1 (0.2)	125 (28.3)	2 (0.9)	2 (0.9)	0	0	4 (1.8)
Decreased appetite	69 (15.6)	43 (9.8)	5 (1.1)	0	117 (26.5)	23 (10.3)	2 (0.9)	1 (0.4)	0	27 (12.1)
Vomiting	79 (17.9)	31 (7.0)	4 (0.9)	0	114 (25.9)	15 (6.7)	4 (1.8)	4 (1.8)	0	23 (10.3)
Headache	62 (14.1)	24 (5.4)	3 (0.7)	NA	89 (20.2)	23 (10.3)	10 (4.5)	1 (0.4)	NA	34 (15.2)
Dysgeusia	60 (13.6)	19 (4.3)	NA	NA	79 (17.9)	5 (2.2)	1 (0.4)	NA	NA	6 (2.7)
Alopecia	60 (13.6)	9 (2.0)	NA	NA	69 (15.9)	4 (1.8)	0	NA	NA	4 (1.8)
Thrombocytopenia	35 (7.9)	19 (4.3)	9 (2.0)	6 (1.4)	69 (15.6)	4 (1.8)	1 (0.4)	0	1 (0.4)	6 (2.7)
Stomatitis	48 (10.9)	17 (3.9)	2 (0.5)	0	67 (15.2)	18 (8.1)	5 (2.2)	0	0	23 (10.3)
Constipation	47 (10.7)	10 (2.3)	3 (0.7)	0	60 (13.6)	26 (11.7)	3 (1.3)	1 (0.4)	0	30 (13.5)
ALT increased	23 (5.2)	18 (4.1)	17 (3.9)	1 (0.2)	59 (13.4)	5 (2.2)	3 (1.3)	4 (1.8)	0	12 (5.4)
Cough	44 (10.0)	15 (3.4)	0	NA	59 (13.4)	21 (9.4)	4 (1.8)	0	NA	25 (11.2)
Pruritus	49 (11.1)	8 (1.8)	0	NA	57 (12.9)	12 (5.4)	1 (0.4)	0	NA	13 (5.8)
Dizziness	45 (10.2)	7 (1.6)	3 (0.7)	NA	55 (12.5)	11 (4.9)	2 (0.9)	0	NA	13 (5.8)
AST increased	25 (5.7)	19 (4.3)	10 (2.3)	0	54 (12.2)	7 (3.1)	2 (0.9)	6 (2.7)	0	15 (6.7)
Blood creatinine increased	27 (6.1)	21 (4.8)	4 (0.9)	0	52 (11.8)	1 (0.4)	0	0	0	1 (0.4)

Continued

	Abemaciclib + Fulvestrant N=441					Placebo + Fulvestrant N=223				
	CTCAE Grade									
Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	All	Grade 1	Grade 2	Grade 3	Grade 4	All
Arthralgia	34 (7.7)	16 (3.6)	1 (0.2)	NA	51 (11.6)	24 (10.8)	7 (3.1)	1 (0.4)	NA	32 (14.3)
Oedema peripheral	41 (9.3)	10 (2.3)	0	NA	51 (11.6)	12 (5.4)	3 (1.3)	0	NA	15 (6.7)
Rash	35 (7.9)	9 (2.0)	5 (1.1)	0	49 (11.1)	8 (3.6)	2 (0.9)	0	0	10 (4.5)
Upper respiratory tract infection	NA	49 (11.1)	0	0	49 (11.1)	1 (0.4)	14 (6.3)	2 (0.9)	0	17 (7.6)
Dyspnea	22 (5.0)	14 (3.2)	11 (2.5)	1(0.2)	48 (10.9)	15 (6.7)	7 (3.1)	3 (1.3)	0	25 (11.2)
Pyrexia	38 (8.6)	7 (1.6)	2 (0.5)	1 (0.2)	48 (10.9)	10 (4.5)	2 (0.9)	1 (0.4)	0	13 (5.8)
Muscular weakness	23 (5.2)	20 (4.5)	4 (0.9)	NA	47 (10.7)	10 (4.5)	3 (1.3)	0	NA	13 (5.8)
Hot flush	39 (8.8)	7 (1.6)	0	NA	46 (10.4)	15 (6.7)	7 (3.1)	0	NA	22 (9.9)
Weight decreased	22 (5.0)	23 (5.2)	1 (0.2)	NA	46 (10.4)	3 (1.3)	1 (0.4)	1 (0.4)	NA	5 (2.2)
Back pain	24 (5.4)	15 (3.4)	3 (0.7)	NA	42 (9.5)	14 (6.3)	12 (5.4)	2 (0.9)	NA	28 (12.6)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; NA = not applicable per CTCAE; N = number of patients in the safety population; n = number of patients in the specified category; TEAE = treatment-emergent adverse event.

Source: home/lillyce/prd/ly2835219/i3y_mc_jpbl/csr1/programs_nonsdd/tfl_output/ae_pt_345_ly.rtf

Source: EMA Public Assessment Report (EMA/551438/2018), page 108/133[6]

6.4 Ongoing Trials

None identified.

7 SUPPLEMENTAL QUESTIONS

The following supplemental issues were identified during development of the review protocol as relevant to the pCODR review of abemaciclib for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2–) advanced or metastatic breast cancer:

The following supplemental issues were identified during development of the review protocol as relevant to the pCODR review of abemaciclib for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2–) advanced or metastatic breast cancer:

- Issue 1: Summary and critical appraisal of the manufacturer-submitted network meta-analysis of interventions for loco-regionally recurrent or metastatic breast cancer patients comparable to the MONARCH 3 trial patient population (*Endocrine-Naïve/Sensitive)*
- Issue 2: Summary and critical appraisal of the manufacturer-submitted network meta-analysis of interventions for advanced or metastatic breast cancer patients comparable to the MONARCH 2 trial patient population (*Endocrine-Resistant)*

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

7.1 Summary and critical appraisal of the manufacturer-submitted network meta-analysis of interventions for loco-regionally recurrent or metastatic breast cancer patients comparable to the MONARCH 3 trial patient population (Endocrine-Naïve/Sensitive)

7.1.1 Objective

The Submitter provided a systematic literature review and network meta-analysis (NMA) to estimate the relative treatment effects for abemaciclib plus a non-steroidal aromatase inhibitor (anastrozole or letrozole; ANAS/LTZ) compared to alternative treatment options used in clinical practice within a MONARCH 3 aligned (endocrine-naïve/sensitive) patient population.

7.1.2 Methods

A systematic literature review was used to inform the NMA.[54] Searches were first run in December 2015, and update searches were run in March 2017 and January 2018 to identify any additional published data. The latest efficacy data for the MONARCH 3 trial (data cut-off date 3rd November 2017, corresponding to the final PFS analysis) was taken from the Submitter's Clinical Study Report (CSR) addendum.

The population inclusion criteria for the systematic review consisted of: adult females, postmenopausal, ≥50% of study population HR+, ≥80% of study population HER2- or HER status unknown, loco-regionally recurrent or metastatic breast cancer, and limited previous treatment for loco-regionally recurrent or metastatic disease. Studies were excluded if patients were currently receiving or had previously received endocrine therapy for locoregionally recurrent or metastatic breast cancer, or had received prior (neo) adjuvant endocrine therapy with a disease-free interval ≤12 months from completion of treatment. Studies were also excluded if >10% of whole study population were currently receiving or have previously received chemotherapy for loco-regionally recurrent or metastatic breast cancer. The systematic review identified 20 primary studies.

The NMA that was conducted in a Bayesian framework included studies that reported at least one endpoint of interest. The endpoints assessed included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and clinical benefit rate (CBR). AEs and HRQoL endpoints were also considered to be relevant endpoints; however, due to inconsistencies in reporting of AE endpoints and a lack of reporting of HRQoL data, the evidence related to these outcomes were not considered to be informative. Therefore, the NMA included only the aforementioned efficacy endpoints.

The reference treatment for the analysis was chosen to be ANAS/LTZ, as this was the comparator arm of the MONARCH 3 trial. The following comparators were considered to be relevant to MONARCH 3 aligned patients and included in the NMA:

- ABE 150mg + ANAS 1mg/LTZ 2.5mg (ABE-ANAS/LTZ)
- ANAS 1mg/LTZ 2.5mg (ANAS/LTZ)
- Exemestane 25mg (EXE)
- Fulvestrant 250mg and 500mg (FUL)
- Palbociclib 125mg + ANAS 1mg/LTZ 2.5mg (PAL-ANAS/LTZ)
- Ribociclib 600mg + ANAS 1mg/LTZ 2.5mg (RIBO-ANAS/LTZ)
- Megestrol acetate 160mg (MGA)
- Tamoxifen 20mg or 40mg (TMX)
- Toremifene 60mg or 200mg (TOR)

More details about the NMA methodology are as follows:

- For the binary endpoints (ORR and CBR), the model codes from the NICE technical support document 2 for binary endpoints (using a logit link) was used;[55] and the treatment effect was measured as an odds ratio (OR).
- For the survival endpoints (PFS and OS), the model code in Woods 2010[56] was used, which allowed for the inclusion of binary data or median survival data where hazard ratios (HR) were not reported in the study publication.
- Both fixed effects and random effects models were employed for each endpoint. The best fitting model was determined using the Deviance Information Criterion (DIC).
- Missing data was imputed according to the nature of missing data.
- An assessment of the proportional hazards assumption for PFS and OS showed that the assumption held across the majority of studies based on the following assessment methods: the log cumulative hazard plots, Schoenfeld residual plots, and weighted residual test based on standardized Schoenfeld residuals.
- For the three closed loops in the evidence network, the Bucher method was used to assess inconsistency between the direct and indirect evidence.
- Between-study heterogeneity was assessed using a qualitative comparison of study and population characteristics. The patient populations were broadly similar for a number of characteristics (e.g. age, post-menopausal status and performance status). However, there were differences across the studies that could impact comparability of the MONARCH 3 trial with other included studies. Methods to adjust for heterogeneity (e.g., using meta-regression) were not considered to be feasible based on the limited study data available.

7.1.3 Findings

A total of 18 studies met the criteria for inclusion in this NMA (Table 7.1).

Table 7.1: Studies included in the network meta-analysis of studies connected to the MONARCH 3 trial

Author Year (primary publication)	Trial name	Intervention (ITT N)	Connected to network of evidence?				
			PFS	OS	ORR	CBR	CR
Allegra 1985	-	MGA (65), TMX20 (66)	✗	✗	✓	✗	✓
Robertson 2016	FALCON	ANAS (232), FUL500 (230)	✓	✗	✗	✗	✗
Robertson 2009	FIRST	ANAS (103), FUL500 (102)	✗	✓	✓	✓	✗
Gill 1993	-	MGA (60), TMX40 (58)	✗	✓	✓	✗	✓
Hayes 1995	-	TMX20 (215), TOR60 (221), TOR200 (212)	✗	✓	✓	✗	✓
Howell 2004	-	FUL250 (313), TMX20 (274)	✓	✓	✓	✓	✓
Iwata 2013	-	EXE (149), ANAS (149)	✗	✓	✓	✓	✓
Milla-Santos 2001	-	TOR60 (106), TMX40 (111)	✗	✓	✓	✗	✓
Milla-Santos 2003	-	ANAS (121), TMX40 (117)	✗	✓	✓	✓	✓
Hortobagyi 2016	MONALEESA-2	RIBO-LTZ (334), LTZ (334)	✓	✓	✓	✓	✓
Goetz 2017	MONARCH 3	ABE-ANAS/LTZ (328), ANAS/LTZ (165)	✓	✓	✓	✓	✓
Mouridsen 2001	-	LTZ (453), TMX20 (454)	✗	✓	✓	✓	✓
Muss 1985	-	MGA (69), TMX20 (67)	✓	✓	✓	✗	✓
Pyrhonen 1997	Nordic	TOR60 (214), TMX40 (201)	✗	✓	✓	✗	✓
Finn 2015	PALOMA-1/TRIO-18	PAL-LTZ (84), LTZ (81)	✓	✓	✓	✓	✓
Finn 2016	PALOMA-2	PAL-LTZ (444), LTZ (222)	✓	✗	✓	✓	✗
Paterson 1990	-	TMX20 (79), MGA (77)	✗	✓	✓	✗	✓
Bonneterre 2001	TARGET and North American	ANAS (511), TMX20 (510)	✓	✓	✓	✓	✓

ABE: Abemaciclib; ANAS: Anastrozole; CBR: Clinical benefit rate; CR: Complete response, EXE: Exemestane; FUL: Fulvestrant; LTZ: Letrozole; MGA: Megestrol acetate; ORR: Objective response rate; OS: Overall survival; PAL: Palbociclib; PFS: Progression-free survival; RIBO: Ribociclib; SLR: Systematic literature review; TMX: Tamoxifen; TOR: Toremifene

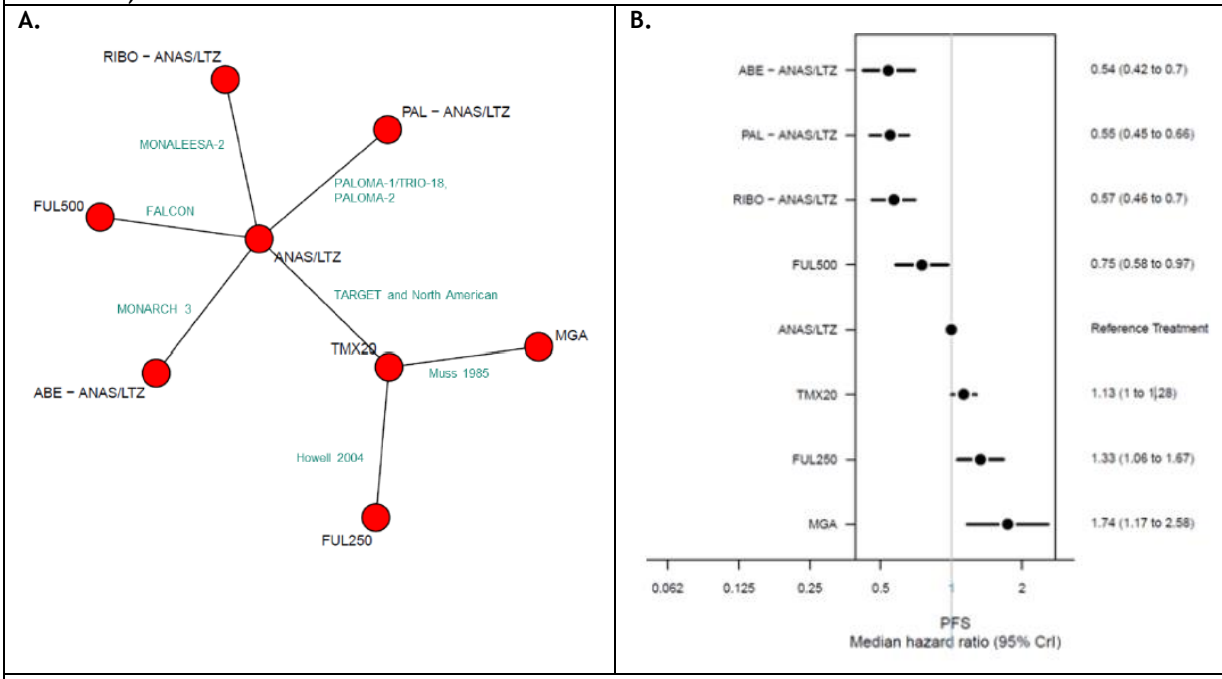
Source: NMA Report (in manufacturer submission), Table 4.1; p. 36/96[54]

A summary of the base case results of the NMA, by efficacy endpoint, is provided below:

Progression-Free Survival (PFS)
Eight trials formed the network of evidence for PFS (Figure 7.1A). When compared to ANAS/LTZ as the reference treatment, ABE-ANAS/LTZ, RIBO-ANAS/LTZ, PAL-ANAS/LTZ and FUL500 showed significantly lower hazard rates of progression or death. On the other hand, significantly higher hazard rates were estimated for FUL250 and MGA (Figure 7.1B).

When ABE-ANAS/LTZ was considered as the reference treatment, significantly PFS hazard rates were estimated for FUL250, MGA, TMX20 and ANAS/LTZ. However, there were no statistically significant differences in PFS hazard rates between ABE-ANAS/LTZ and combination therapies with RIBO-ANAS/LTZ or PAL-ANAS/LTZ (based on wide credible intervals including the null hypothesis value; i.e., HR = 1; Table 7.2).

Figure 7.1: Network meta-analysis of studies connected to MONARCH 3 – PFS (all interventions vs. ANAS/LTZ)



A. PFS network diagram; B. Forest plot of treatment effects relative to ANAS/LTZ for PFS using fixed effect model

Source: NMA Report (in manufacturer submission), Figures 4.1 and 4.2, p.38-39/96[54]

Table 7.2: Network meta-analysis of studies connected to MONARCH 3 – PFS (all interventions vs. ABE-ANAS/LTZ)

Comparator	ABE-ANAS/LTZ
ANAS/LTZ	1.85 (1.43,2.4)
ABE - ANAS/LTZ	1 (1,1)
FUL250	2.47 (1.75,3.48)
FUL500	1.39 (0.97,2)
MGA	3.23 (2.01,5.15)
PAL - ANAS/LTZ	1.01 (0.74,1.39)
RIBO - ANAS/LTZ	1.05 (0.75,1.47)
TMX20	2.09 (1.58,2.78)

**Median hazard ratio and 95% Credible Interval) – fixed effect model*
HR>1 favours ABE-ANAS/LTZ
95% credible intervals including the null hypothesis (i.e. HR=1) indicate lack of a statistically significant difference
Source: Submission documents, Checkpoint materials[53,57]

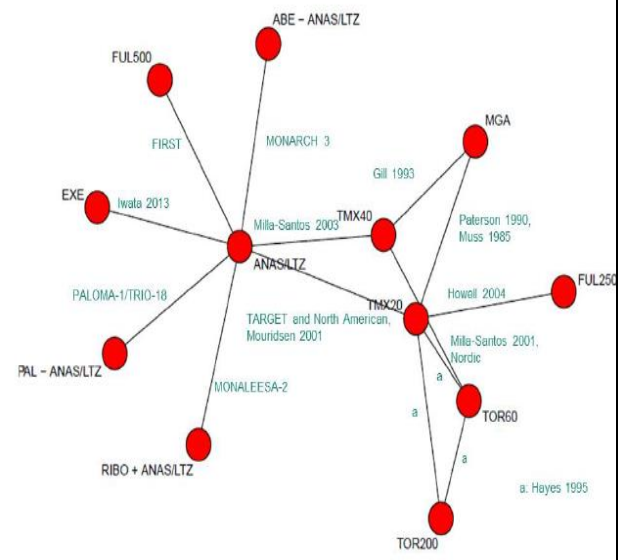
Overall Survival (OS)

Fifteen trials formed the evidence network for OS (Figure 7.2A). The OS data for three trials was immature at the time of analysis (i.e., median OS had not been reached in at least one arm) including the MONALEESA-2 (RIBO-ANAS/LTZ vs. ANAS/LTZ), MONARCH 3 (ABE-ANAS/LTZ vs. ANAS/LTZ) and Iwata 2013 (EXE vs. ANAS/LTZ) trials. Therefore, the results of OS NMA for these trials are uncertain. FUL500 (HR=0.70; 95% CrI 0.46, 1.08), RIBO-ANAS/LTZ (HR=0.75; CrI 0.47, 1.17) and PAL-ANAS/LTZ (HR=0.90; CrI 0.57, 1.40) had numerically lower hazards of death

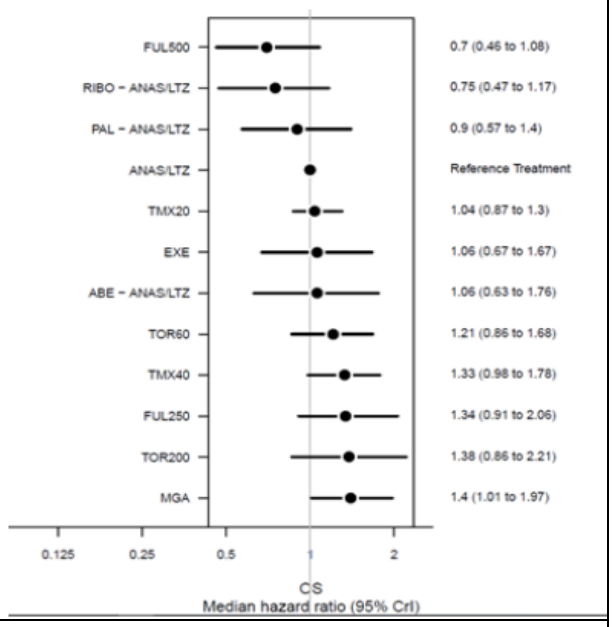
compared to ANAS/LTZ; however, the estimated HRs were not statistically significant. A significantly higher hazard of death was reported for MGA compared to ANAS/LTZ (HR=1.40, 95% CrI 1.07, 1.97) (Figure 7.2B). NMA comparisons against ABE-ANAS/LTZ showed no OS difference between ABE-ANAS/LTZ and other comparators (Table 7.3)

Figure 7.2: Network meta-analysis of studies connected to MONARCH 3 – OS (all interventions vs. ANAS/LTZ)

A.



B.



A. OS network diagram; B. Forest plot of treatment effects relative to ANAS/LTZ for OS using random effects model
[Trials with immature OS: MONALEESA-2, MONARCH 3, and Iwata 2013]
Source: NMA Report (in manufacturer submission), Figures 4.3 and 4.4, p.40-41/96[54]

Table 7.3: Network meta-analysis of studies connected to MONARCH 3 – OS (all interventions vs. ABE-ANAS/LTZ)

Comparator	ABE-ANAS/LTZ
ANAS/LTZ	0.95 (0.57,1.58)
ABE - ANAS/LTZ	1 (1,1)
EXE	1 (0.5,1.99)
FUL250	1.27 (0.67,2.48)
FUL500	0.66 (0.34,1.29)
MGA	1.32 (0.72,2.46)
PAL - ANAS/LTZ	0.85 (0.43,1.68)
RIBO - ANAS/LTZ	0.71 (0.36,1.4)
TMX20	0.99 (0.58,1.73)
TMX40	1.25 (0.69,2.27)
TOR200	1.3 (0.65,2.62)
TOR60	1.14 (0.62,2.1)

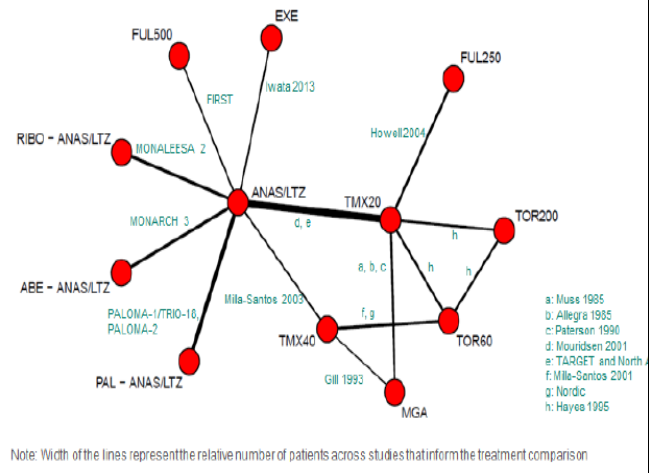
**Median hazard ratio and 95% Credible Intervals – random effects model*
HR>1 favours ABE-ANAS/LTZ
95% credible intervals including the null hypothesis (i.e. HR=1) indicate lack of a statistically significant difference
Source: Submission documents, Checkpoint materials[53,57]

Objective Response Rate (ORR)

Seventeen studies formed the evidence network for ORR (Figure 7.3A). No statistically significant OR estimates were observed for any treatment compared to ANAS/LTZ (Figure 7.3B). Similarly, NMA comparisons against ABE-ANAS/LTZ showed no ORR difference between ABE-ANAS/LTZ and other treatments, including combination regimens with RIBO-ANAS/LTZ and PAL-ANAS/LTZ (Table 7.4).

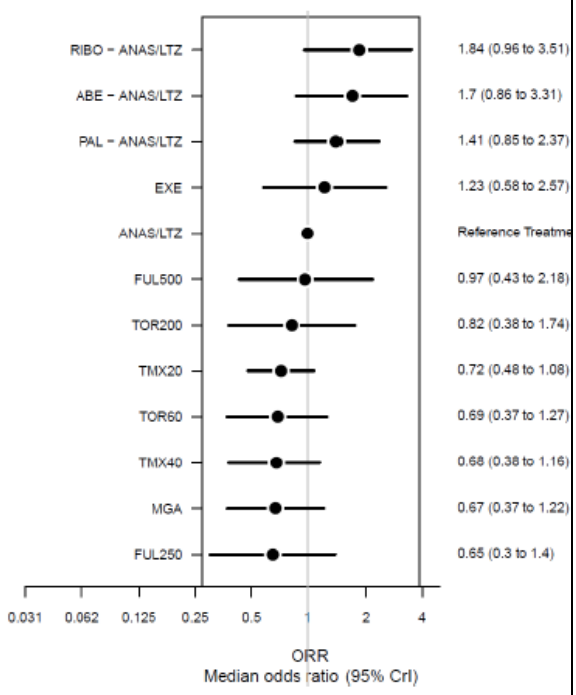
Figure 7.3: Network meta-analysis of studies connected to MONARCH 3- ORR (all interventions vs. ANAS/LTZ)

A.



Note: Width of the lines represent the relative number of patients across studies that inform the treatment comparison

B.



A.ORR network diagram; B. Forest plot of treatment effects relative to ANAS/LTZfor ORR using random effects model

Source: NMA Report (in manufacturer submission), Figures 4.5 and 4.6, p.42-43/96[54]

Table 7.4: Network meta-analysis of studies connected to MONARCH 3 – ORR (all interventions vs. ABE-ANAS/LTZ)

Comparator	ABE-ANAS/LTZ
ANAS/LTZ	0.59 (0.3,1.16)
ABE - ANAS/LTZ	1 (1,1)
EXE	0.72 (0.27,1.97)
FUL250	0.38 (0.14,1.07)
FUL500	0.57 (0.2,1.64)
MGA	0.4 (0.16,0.98)
PAL - ANAS/LTZ	0.83 (0.36,1.95)
RIBO - ANAS/LTZ	1.08 (0.43,2.75)
TMX20	0.42 (0.19,0.93)
TMX40	0.4 (0.16,0.94)
TOR200	0.48 (0.17,1.34)
TOR60	0.41 (0.16,1.02)

**Median odds ratio and 95% Credible Interval) – random effects model*

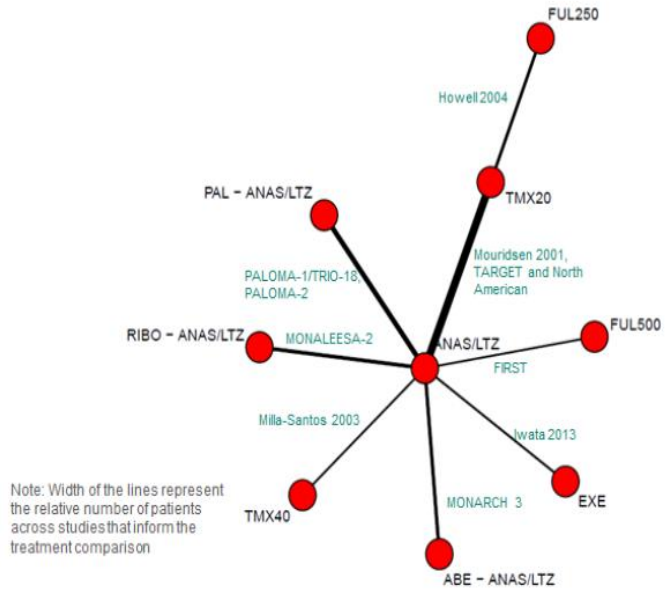
OR<1 favours ABE-ANAS/LTZ
95% credible intervals including the null hypothesis (i.e. OR=1) value indicate lack of a statistically significant difference
Source: Submission documents, Checkpoint materials[53,57]

Clinical Benefit Rate (CBR)

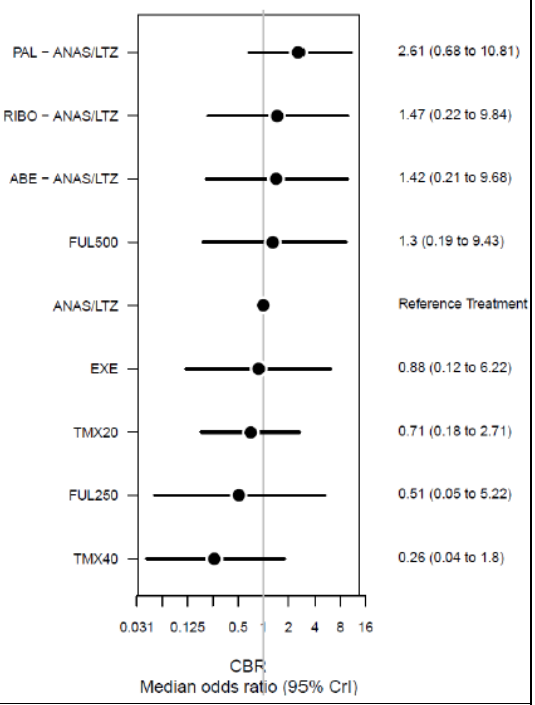
Ten studies formed the evidence network for CBR (Figure 7.4A).The results of the NMA showed no statistically significant OR estimates for any treatment compared to ANAS/LTZ (Figure 7.4B). All CBR comparisons against combination therapy with ABE- ANAS/LTZ were also statistically non-significant (Table 7.5).

Figure 7.4: Network meta-analysis of studies connected to MONARCH3 – CBR (all interventions vs. ANAS/LTZ)

A.



B.



A.CBR network diagram; B. Forest plot of treatment effects relative to ANAS/LTZ for CBR using random effects model
Source: NMA Report (in manufacturer submission), Figures 4.7 and 4.8, p.44-45/96[54]

Table 7.5: Network meta-analysis of studies connected to MONARCH 3 – CBR (all interventions vs. ABE-ANAS/LTZ)

Comparator	ABE-ANAS/LTZ
ANAS/LTZ	0.71 (0.1,4.77)
ABE - ANAS/LTZ	1 (1,1)
EXE	0.62 (0.04,9.56)
FUL250	0.36 (0.02,7.42)
FUL500	0.92 (0.06,14.56)
PAL - ANAS/LTZ	1.84 (0.18,20.68)
RIBO - ANAS/LTZ	1.04 (0.07,15.64)
TMX20	0.5 (0.05,5.16)
TMX40	0.18 (0.01,2.79)

**Median odds ratio and 95% Credible Intervals – random effects model*
OR<1 favours ABE-ANAS/LTZ
95% credible intervals including the null hypothesis (i.e. OR=1) value indicate lack of a statistically significant difference
Source: Submission documents, Checkpoint materials[53,57]

7.1.4 Summary and conclusions

The quality of the submitted NMA assessed according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[58] Details of the critical appraisal are presented in Table 7.6.

Table 7.6: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis† (network meta-analysis of studies connected to MONARCH 3 – Endocrine-Naïve/Sensitive)

ISPOR Questions		Details and Comments
1.	Is the population relevant?	**Yes**. The study populations of the studies included in the NMA were relevant to the indication under review (MONARCH 3-alighned population).
2.	Are any critical interventions missing?	**No.** all comparators identified in the systematic review that were considered to be clinically relevant to MONARCH 3-aligned patients were included in the NMA.
3.	Are any relevant outcomes missing?	**Yes, in part.** The following outcomes were assessed: OS, PFS, ORR and CBR. Other relevant outcomes such quality of life, and safety results were excluded from the submitted NMA, due to inconsistencies in reporting of AE endpoints and a lack of reporting of HRQoL data.
4.	Is the context (e.g., settings and circumstances) applicable to your population?	**Yes**. The settings of the included trials were relevant to that in this pCODR review.
5.	Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes**. For the purpose of this pCODR submission, the Submitter conducted a systematic literature review of randomized controlled trials. The Submitter provided a detailed report of the systematic literature review process used in the NMA. The report shows indicates that the Submitter took adequate steps to ensure an unbiased selection of studies for inclusion in their analysis.
6.	Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**Yes**. The submitted NMAs included studies that reported at least one endpoint of interest. A connected network of evidence was constructed for each efficacy outcome by linking treatments.
7.	Is it apparent that poor quality studies were included thereby leading to bias?	**No.** Based on the Submitter's systematic review report, Risk of Bias assessment was performed using the domains recommended in the NICE guide to the methods of technology appraisal. The results of the quality assessment of individual trials were provided in the submitted report. All studies were assessed as being of good quality with an acceptable risk of bias (low or unclear risk of bias).

8.	Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No.** There was no selective reporting of outcomes.
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**. The patient populations were broadly similar for a number of characteristics (e.g. age, post-menopausal status and performance status). However, There were differences across the studies (in terms of HR+/HER2- status, disease-free interval, site of disease, prior chemotherapy, prior endocrine therapy, and visceral involvement at baseline) that could impact comparability of the MONARCH 3 trial with other included studies.
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**. In order to show between-study similarities, the - submitted NMA report described the distribution of key baseline characteristics of the study populations along with a description of study design characteristics. Between-study heterogeneity was assessed using a qualitative comparison of study and population characteristics.
11.	Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Yes**. The indirect comparisons were based on relative effect measures. For the binary endpoints (ORR and CBR), the model codes from the NICE technical support document 2 for binary endpoints (using a logit link) was used,[55] and the treatment effect was measured as an odds ratio. For the survival endpoints (PFS and OS), the model code in Woods 2010[56] was used, which allowed for the inclusion of binary data or median survival data where hazard ratios were not reported in the study publication
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?	**Yes.** For Loops in all networks, inconsistency was assessed using inconsistency models and compared against models assuming consistency.
13.	In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Yes.** For the three closed loops in the evidence network, the Bucher method was used to assess inconsistency between the direct and indirect evidence.
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?	**Not applicable**. The results form inconsistency assessment showed in all cases of the estimate of inconsistency was statistically non-significant.
15.	Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes.** Both fixed effects and random effects models were employed for each endpoint. The best fitting model was determined using the Deviance Information Criterion (DIC**).**
16.	If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Yes.**
17.	If there are indications of heterogeneity, were subgroup	**No.** No subgroup analyses were conducted to address the heterogeneity. Methods to adjust for heterogeneity (e.g., using

	analyses or meta-regression analysis with pre-specified covariates performed?	meta-regression) were also not considered to be feasible based on the limited study data available.
18.	Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes.** In the Submitter's NMA report, an evidence network was graphically presented for each efficacy outcome.
19.	Are the individual study results reported?	**Yes**. The effect estimates of all outcomes included in the NMA were provided in the submitted systematic review and NMA reports.
20.	Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**Yes.** The Submitter's original NMA report provided the pairwise direct comparisons (where available) along with indirect results for each of the competing interventions versus an aromatase inhibitor (i.e., ANAS/LTZ) as the reference treatment. During the review process, and following pCODR's request for additional information, Submitter provided a table of pairwise comparisons that showed relative effect of all treatment options included in the network meta-analyses versus abemaciclib + ANAS/LTZ as the reference treatment.
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% CrI) were reported for estimates of effect.
22.	Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**Yes.** In the submitted report, the probabilistic ranking plots were presented for all comparators that were included in the NMA.
23.	Is the impact of important patient characteristics on treatment effects reported?	**No.** No subgroup or sensitivity analyses were performed based on specific patient characteristics. In their report, the Submitter acknowledged that a sensitivity analysis, restricting to HR+ / HER2- studies or studies reporting subgroup data for this population, could potentially be conducted.
24.	Are the conclusions fair and balanced?	**Yes.** The submitted NMA concluded that that combination of CDK4&6 inhibitors and endocrine therapy regimens —ABEANAS/ LTZ, PAL-ANAS/LTZ and RIBO-ANAS/LTZ — provided greater treatment benefit compared to single agent endocrine therapy regimens for PFS, ORR and CBR. It was also noted in the conclusions section that the results of the NMA needed to be interpreted with caution due to the between study heterogeneity and immature OS data.
25.	Were there any potential conflicts of interest?	**Not reported.**
26.	If yes, were steps taken to address these?	**Not applicable.**
ALK = anaplastic large-cell lymphoma kinase; **ECOG PS**= Eastern Cooperative Oncology Group performance score; **EGFR =** epidermal growth factor receptor; **ISPOR** = International Society For Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparison; **NMA**= network meta-analysis; **NSCLC**= non-small cell lung cancer; **NSQ** = non squamous**; OS** = overall survival; **PD-L1** = programmed death-ligand1**PFS** = progression-free survival; † Adapted from Jansen, Value Health. 2014;17(2):157-73[58]		

Conclusion

The Submitter provided a systematic literature review and network meta-analysis (NMA) to estimate the relative treatment effects for abemaciclib + AI (ANAS/LTZ) compared to alternative treatment options used in clinical practice within a MONARCH 3 aligned (endocrine-naïve/sensitive) patient population. The NMA was conducted in a Bayesian framework and assessed efficacy outcomes (i.e., PFS, OS, ORR, and CBR). The analysis results showed that combination CDK4&6 inhibitors and endocrine therapy regimens ABE-ANAS/LTZ, PAL-ANAS/LTZ and RIBO-ANAS/LTZ provided greater treatment benefit compared to single agent endocrine therapy regimens (including ANAS/LTZ) for PFS, ORR and CBR. No statistically significant differences in efficacy outcomes were found between ABE-ANAS/LTZ, PAL-ANAS/LTZ and RIBO-ANAS/LTZ. However, these NMA results should be interpreted with caution given the heterogeneity across the studies that could impact their comparability to the MONARCH 3 trial, and the fact that adjusting for heterogeneity was not feasible due to limited data. In addition, the results of NMA for OS remained uncertain owing to immature OS data for a number of the included trials, at the time of analysis.

7.2 Summary and critical appraisal of the manufacturer-submitted network meta-analysis of interventions for advanced or metastatic breast cancer patients comparable to the MONARCH 2 trial patient population (Endocrine-Resistant)

7.2.1 Objective

The Submitter provided a systematic literature review and network meta-analysis (NMA) to estimate the relative treatment effects for abemaciclib + fulvestrant compared to alternative treatment options used in clinical practice for patients progressing on or after prior endocrine therapy within a MONARCH 2 aligned patient population.

7.2.2 Methods

A systematic literature review was used to inform the NMA.[54] Searches were first run in December 2015, and update searches were run in March 2017 and January 2018 to identify any additional published data. Due to the specificity of the MONARCH 2 study characteristics, the eligibility criteria for the systematic review was broadened and allowed mixed populations to be included with regards to some baseline characteristics. Studies were included in the Submitter's systematic review if:

- ≥50% of the population were HR+ (all patients were HR+ in MONARCGH 2)
- Patients' HER2 status was not reported (all MONARCH 2 patients were HER2-)
- Exposure to prior endocrine treatment was not reported (all MONARCH 2 patients had progressed on endocrine therapy)
- Menopausal status was not reported (All MONARCH 2 patients were postmenopausal)
- Patients had received one line of chemotherapy for metastatic disease (no MONARCH 2 patients had chemotherapy for advanced or metastatic disease)

The systematic review identified 22 primary publications, including 20 studies reporting on endocrine therapy and/or targeted therapies and nine studies reporting data on chemotherapy and/or targeted therapies. No studies were identified that compared endocrine therapy with chemotherapy.

The NMA that was conducted in a Bayesian framework included studies that reported at least one endpoint of interest. The endpoints assessed included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and clinical benefit rate (CBR). AEs and HRQoL endpoints were also considered to be relevant endpoints; however, due to inconsistencies in

reporting of AE endpoints and a lack of reporting of HRQoL data, the evidence related to these outcomes were not considered to be informative. Therefore, the NMA included only the aforementioned efficacy endpoints.

The reference treatment for the analysis was chosen to be fulvestrant 500 mg, as this was the comparator arm of the MONARCH 2 trial. However, not all comparators identified in the systematic review were considered clinically relevant in real-world practice. The following comparators were considered to be relevant to MONARCH 2 aligned patients and included in the NMA:

- Abemaciclib + fulvestrant (ABE-FUL)
- Anastrozole 1mg (ANAS 1)
- Anastrozole 10mg (ANAS 10)
- Letrozole 2.5mg (LTZ 2.5)
- Exemestane (EXE)
- Exemestane + everolimus (EXE-EVE)
- Fulvestrant 250mg (FUL 250)
- Fulvestrant 500mg FUL 500
- Palbociclib + fulvestrant 500mg (PAL-FUL)
- Tamoxifen (TMX)

More details about the NMA methodology are as follows:

- For the binary endpoints (ORR and CBR), the model codes from the NICE technical support document 2 for binary endpoints (using a logit link) was used;[55] and the treatment effect was measured as an odds ratio (OR).
- For the survival endpoints (PFS and OS), the model code in Woods 2010[56] was used, which allowed for the inclusion of binary data or median survival data where hazard ratios (HR) were not reported in the study publication.
- Both fixed effects and random effects models were employed for each endpoint. The best fitting model was determined using the Deviance Information Criterion (DIC).
- Missing data was imputed according to the nature of missing data.
- An assessment of the proportional hazards assumption for PFS and OS showed that the assumption held across the majority of studies based on the following assessment methods: the log cumulative hazard plots, Schoenfeld residual plots, and weighted residual test based on standardized Schoenfeld residuals.
- For Loops in all networks, inconsistency was assessed using inconsistency models and compared against models assuming consistency. The inconsistency assessment showed strong evidence of inconsistency across the endpoints assessed.
- Between-study heterogeneity was assessed using a qualitative comparison of study and population characteristics. The patient populations were broadly similar for a number of characteristics (e.g. age, post-menopausal status and performance status). However, there were differences across the studies that could impact comparability of the MONARCH 2 trial with other included studies. Methods to adjust for heterogeneity (e.g., using meta-regression) were not considered to be feasible based on the limited study data available.
- A sensitivity analysis using a subpopulation of the PALOMA 3 trial assessed the impact of prior chemotherapy in the metastatic setting on the results of the NMA.

7.2.3 Findings

A total of 19 studies met the criteria for inclusion in the NMA (Table 7.7).

Table 7.7: Studies included in the network meta-analysis of studies connected to the MONARCH 2 trial

Author Year (primary publication)	Trial name	Intervention (ITT N)	Connected to network of evidence?			
			ORR	CBR	OS	PFS
Baselga 2012	BOLERO-2	EXE-EVE (485), EXE (239)	✓	✓	✓	✓
Buzdar 1997	-	ANAS 1 mg (128), ANAS 10 mg (130), MGA 160 mg (128)	✓	✓	✓	✓
Buzdar 2001	-	LTZ 0.5 mg (202), LTZ 2.5 mg (199), MGA 160 mg (201)	✓	×	✓	✓
Campos 2009	-	EXE (65), ANAS 1 mg (65)	×	✓	✓	✓
Chia 2008	EFECT	FUL 250 mg (351), EXE (342)	✓	✓	×	×
Di Leo 2010	CONFIRM	FUL 500 mg (362), FUL 250 mg (374)	✓	✓	✓	✓
Dombernowsky 1998	-	LTZ 0.5 mg (188), LTZ 2.5 mg (174), MGA 160 mg (189)	✓	✓	✓	×
Nishimura 2017	Hi-FAIR fx	FUL 500 mg (52), TOR (53)	✓	✓	✓	✓
Howell 2002	-	FUL 250 mg (222), ANAS 1 mg (229)	✓	✓	✓	✓
Johnston 2013	SoFEA	FUL 250 mg (231), EXE (249)	✓	✓	✓	✓
Jonat 1996	-	ANAS 1 mg (135), ANAS 10 mg (118), MGA 160 mg (125)	✓	✓	✓	✓
Kaufmann 2000	-	EXE (366), MGA 160 mg (403)	✓	✓	✓	×
Muss 1990	-	MGA 160 mg (86), MGA 800 mg (84)	✓	×	✓	×
Osborne 2002	Trial 0021	FUL 250 mg (206), ANAS 1 mg (194)	✓	✓	✓	✓
Rose 2003	-	LTZ 2.5 mg (356), ANAS 1 mg (357)	✓	✓	✓	×
Sledge 2017	MONARCH 2	ABE-FUL (446), FUL 500 mg (223)	✓	✓	✓	✓
Turner 2015	PALOMA 3	PAL-FUL (347), FUL 500 mg (174)	✓	✓	✓	✓
Yamamoto 2013	-	TOR (46), EXE (45)	✓	✓	✓	✓
Zhang 2016	-	FUL 500 mg (111), FUL 250 mg (110)	✓	✓	×	✓

ABE: Abemaciclib; ANAS: Anastrozole; CBR: Clinical benefit rate; EVE: Everolimus; EXE: Exemestane; FUL: Fulvestrant; LTZ: Letrozole; mg: milligrams; MGA: Megestrol acetate; NMA: Network meta-analysis; ORR: Objective response rate; OS: Overall survival; PAL: Palbociclib; PFS: Progression-free survival; SLR: Systematic literature review; TOR: Toremifene

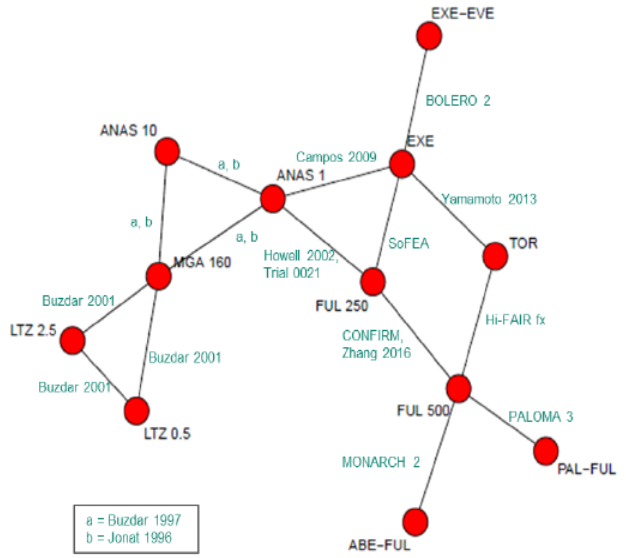
Source: NMA Report (in manufacturer submission), Table 4.1; p. 32/104[54]

A summary of the base case results of the NMA, by efficacy endpoint, is provided below:

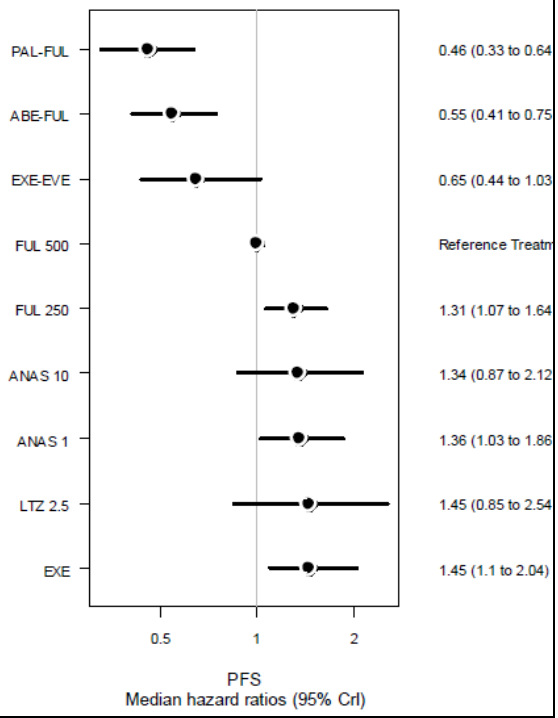
Progression-Free Survival (PFS)
Fourteen trials formed the network of evidence for PFS (Figure 7.5A). When compared to FUL 500, ABE-FUL and PAL-FUL both showed a significantly lower hazard rate of progression or death. FUL 250, ANAS 1 and EXE had significantly higher hazard rates of progression or death compared to FUL 500 (Figure 7.5B). NMA results, with ABE- ABE-FUL as the reference treatment, showed no statistically significant difference in PFS hazard rate between ABE-FUL and PAL-FUL (Table 7.8).

Figure 7.5: Network meta-analysis of studies connected to MONARCH 2 – PFS (all interventions vs. FUL500)

A.



B.



A. PFS network diagram; B. Forest plot of treatment effects relative to FUL 500 for PFS using random effects model
Source: NMA Report (in manufacturer submission), Figures 4.1 and 4.2, p.34-35/104[54]

Table 7.8: Network meta-analysis of studies connected to MONARCH 2 – PFS (all interventions vs. ABE-FUL)*

Comparator	ABE-FUL
FUL 500	1.81 (1.33,2.46)
ABE-FUL	1 (1,1)
ANAS 1	2.46 (1.63,3.82)
ANAS 10	2.42 (1.43,4.22)
EXE	2.63 (1.76,4.2)
EXE-EVE	1.18 (0.73,2.06)
FUL 250	2.36 (1.65,3.49)
LTZ 0.5	2.12 (1.15,4.02)
LTZ 2.5	2.63 (1.42,4.98)
MGA 160	2.65 (1.6,4.52)
PAL-FUL	0.83 (0.53,1.31)
TOR	1.96 (1.21,3.21)

**Median hazard ratio and 95% Credible Intervals- random effects model*
HR>1 favours ABE-FUL
Source: Submission documents, Checkpoint materials[53,57]

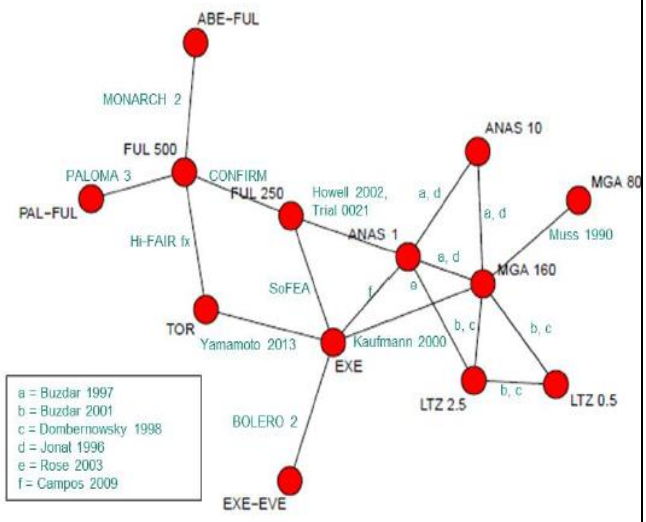
Overall Survival (OS)

Seventeen trials formed the evidence network for OS (Figure 7.6A). The OS data for eight trials was immature at the time of analysis (i.e., median OS had not been reached in at least one arm) including the MONARCH 2 and PALOMA 3 trials. Therefore, the results of NMA for OS were uncertain, with no significant decreases in the OS hazard rates compared to FUL500 (Figure 7.6B).

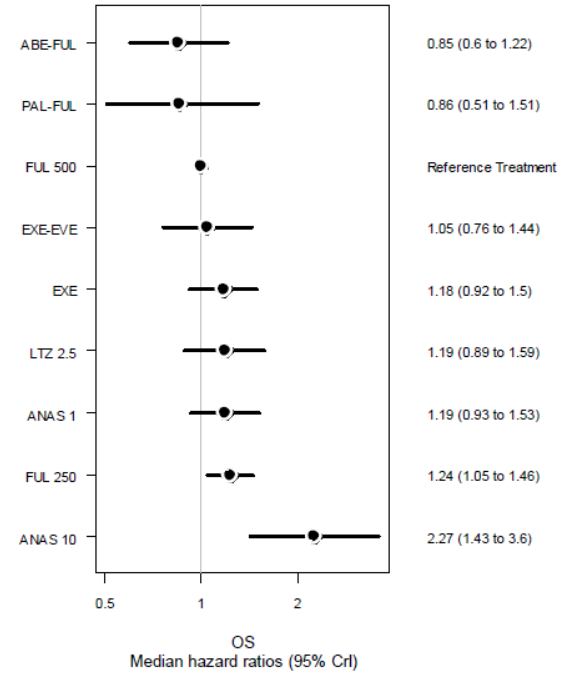
NMA results, with ABE-FUL as the reference treatment, showed that ANAS 10 and MGA 160 had significantly higher hazard rates of death compared to ABE-FUL (Table 7.10).

Figure 7.9: Network meta-analysis of studies connected to MONARCH 2 – OS (all interventions vs. FUL500)

A.



B.



A. OS network diagram; B. Forest plot of treatment effects relative to FUL 500 for OS using fixed effect model
[Trials with immature OS: Buzdar 1997; Hi-FAIR fx; Howell 2002; Jonat 1996; PALOMA 3; Kaufmann 2000; Trial 0021; MONARCH 2]
Source: NMA Report (in manufacturer submission), Figures 4.4 and 4.5, p.38-39/104[54]

Table 7.10: Network meta-analysis of studies connected to MONARCH 2 – OS (all interventions vs. ABE-FUL)*

Comparator	ABE-FUL
FUL 500	1.17 (0.82,1.67)
ABE-FUL	1 (1,1)
ANAS 1	1.39 (0.9,2.16)
ANAS 10	2.66 (1.48,4.75)
EXE	1.38 (0.89,2.12)
EXE-EVE	1.23 (0.76,1.98)
FUL 250	1.45 (0.98,2.15)
LTZ 0.5	1.5 (0.92,2.45)
LTZ 2.5	1.4 (0.88,2.21)
MGA 160	1.72 (1.09,2.72)
MGA 800	1.13 (0.61,2.1)
PAL-FUL	1.01 (0.53,1.96)
TOR	0.89 (0.51,1.54)

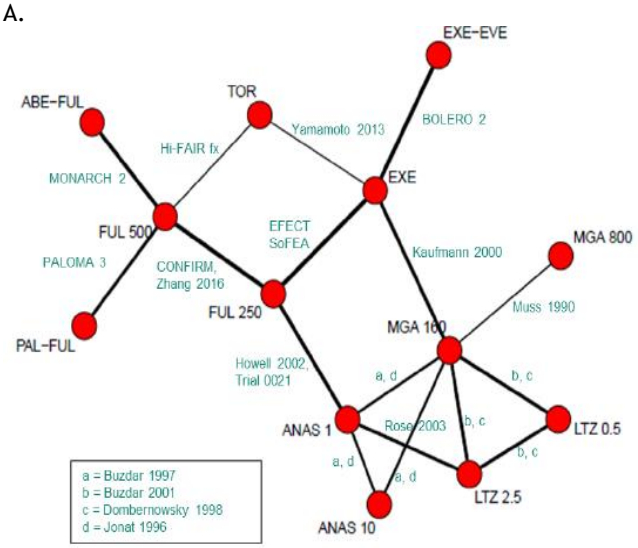
**Median hazard ratio and 95% Credible Intervals – fixed effect model*
HR>1 favours ABE-FUL
Source: Submission documents, Checkpoint materials[53,57]

Objective Response Rate (ORR)

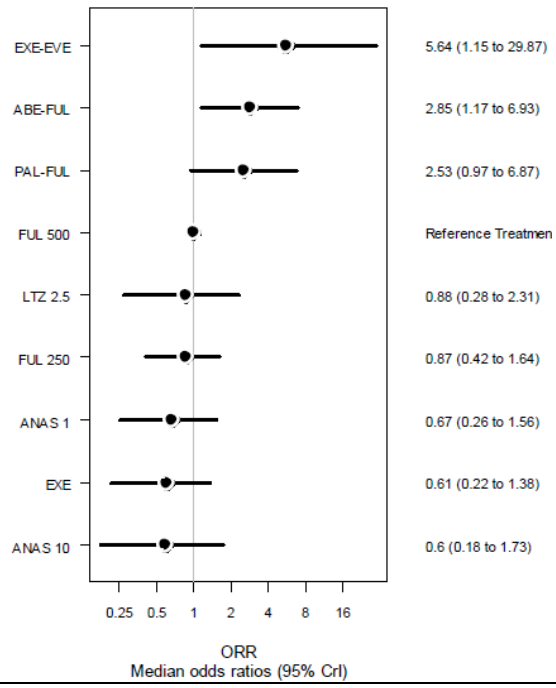
Eighteen studies formed the evidence network for ORR (Figure 7.7A). When compared to FUL 500, EXE-EVE and ABE-FUL showed significantly higher odds of achieving a response compared to FUL 500. No treatment showed a significant reduction in the odds of achieving a response. No other treatment options showed a statistically significant ORR benefits, compared to FUL 500 (Figure 7.7B). With ABE-FUL as the reference treatment, ABE-FUL and PAL-FUL regimens demonstrated comparable objective response rates; however, ABE-FUL had a significantly greater ORR than EXE-EVE (Table 7.11).

Figure 7.7: Network meta-analysis of studies connected to MONARCH 2 – ORR (all interventions vs. FUL500)

A.



B.



A.ORR network diagram; B. Forest plot of treatment effects relative to FUL 500 for ORR using random effects model

Source: NMA Report (in manufacturer submission), Figures 4.6 and 4.7, p.41-42/104[54]

Table 7.11: Network meta-analysis of studies connected to MONARCH 2 – ORR (all interventions vs. ABE-FUL)*

Comparator	ABE-FUL
FUL 500	0.35 (0.14,0.85)
ABE-FUL	1 (1,1)
ANAS 1	0.24 (0.06,0.79)
ANAS 10	0.21 (0.05,0.82)
EXE	0.22 (0.05,0.68)
EXE-EVE	1.99 (0.31,12.59)
FUL 250	0.31 (0.09,0.88)
LTZ 0.5	0.24 (0.05,0.89)
LTZ 2.5	0.31 (0.07,1.11)
MGA 160	0.2 (0.05,0.68)
MGA 800	0.7 (0.11,3.88)
PAL-FUL	0.89 (0.24,3.39)
TOR	0.43 (0.11,1.85)

**Median odds ratio and 95% Credible Intervals - random effects model*
OR<1 favours ABE-FUL

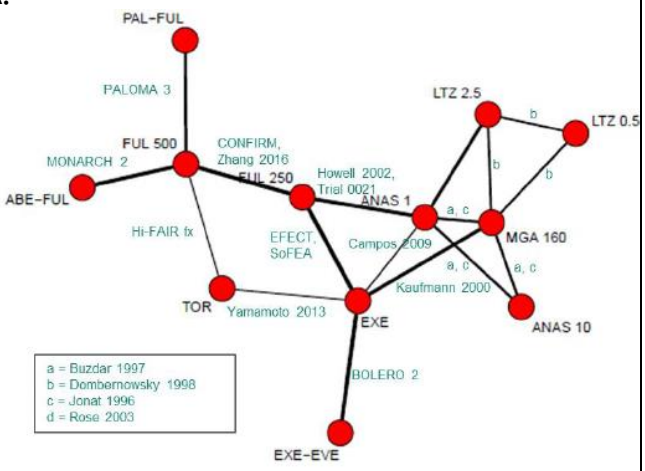
Source: Submission documents, Checkpoint materials[53,57]

Clinical Benefit Rate (CBR)

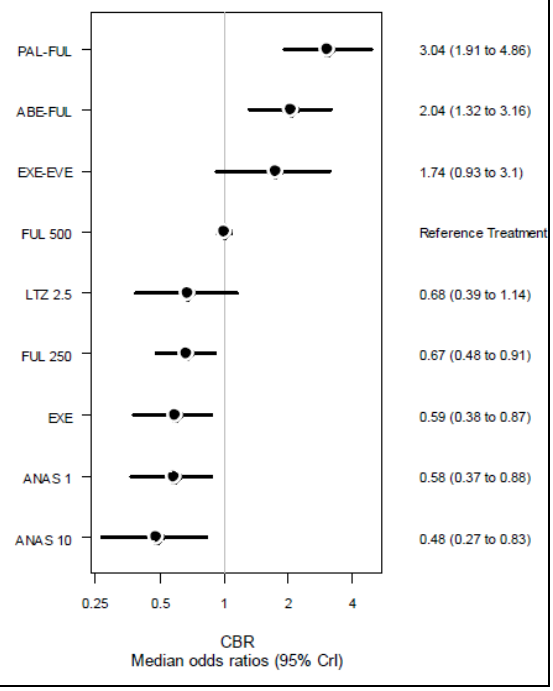
Seventeen studies formed the evidence network for CBR (Figure 7.8A).The results of the NMA showed that PAL-FUL and ABE-FUL had a significantly higher odds of achieving a clinical benefit compared to FUL 500. Based on the estimated relative treatment effects (OR), the CBR for the following treatments was significantly lower than that for FUL 500: FUL 250, EXE, ANAS 1, and ANAS 10 (Figure 7.8B). The NMA results, with ABE-FUL as the reference treatment, showed that, ABE-FUL and PAL-FUL regimens had comparable clinical benefit rates, and that ABE-FUL was superior to all other treatment options in terms of CBR (Table 7.12).

Figure 7.8: Network meta-analysis of studies connected to MONARCH 2 – CBR (all interventions vs. FUL500)

A.



B.



A.CBR network diagram; B. Forest plot of treatment effects relative to FUL 500 for CBR using random effects model
Source: NMA Report (in manufacturer submission), Figures 4.8 and 4.9, p.44-45/104[54]

Table 7.12: Network meta-analysis of studies connected to MONARCH 2 – CBR (all interventions vs. ABE-FUL)*

Comparator	ABE-FUL
FUL 500	0.49 (0.32,0.76)
ABE-FUL	1 (1,1)
ANAS 1	0.28 (0.15,0.51)
ANAS 10	0.24 (0.12,0.47)
EXE	0.29 (0.15,0.51)
EXE-EVE	0.85 (0.4,1.75)
FUL 250	0.33 (0.19,0.56)
LTZ 0.5	0.22 (0.1,0.47)
LTZ 2.5	0.33 (0.16,0.65)
MGA 160	0.27 (0.14,0.5)
PAL-FUL	1.49 (0.78,2.82)
TOR	0.39 (0.18,0.84)

**Median odds ratio and 95% Credible Intervals - random effects model*
OR<1 favours ABE-FUL
Source: Submission documents, Checkpoint materials[53,57]

7.2.4 Summary and conclusions

The quality of the submitted NMA assessed according to the recommendations made by the ISPOR Task Force on Indirect Treatment Comparisons.[58] Details of the critical appraisal are presented in Table 7.13.

Table 7.13: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis† (network meta-analysis of studies connected to MONARCH 2 – Endocrine-Resistant)

ISPOR Questions		Details and Comments
1.	Is the population relevant?	**Yes**. The study populations of the studies included in the NMA were relevant to the indication under review (MONARCH 2-alighned population).
2.	Are any critical interventions missing?	**No.** all comparators identified in the systematic review that were considered to be clinically relevant for this patient population in real-world practice were included in the NMA.
3.	Are any relevant outcomes missing?	**Yes, in part.** The following outcomes were assessed: OS, PFS, ORR and CBR. Other relevant outcomes such quality of life, and safety results were excluded from the submitted NMA, due to inconsistencies in reporting of AE endpoints and a lack of reporting of HRQoL data.
4.	Is the context (e.g., settings and circumstances) applicable to your population?	**Yes**. The settings of the included trials were relevant to that in this pCODR review.

Table 7.13: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis† (network meta-analysis of studies connected to MONARCH 2 – Endocrine-Resistant)		
	ISPOR Questions	**Details and Comments**
5.	Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes**. For the purpose of this pCODR submission, the Submitter conducted a systematic literature review of randomized controlled trials. The Submitter provided a detailed report of the systematic literature review process used in the NMA. The report shows indicates that the Submitter took adequate steps to ensure an unbiased selection of studies for inclusion in their analysis.
6.	Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**Yes**. The submitted NMAs included studies that reported at least one endpoint of interest. A connected network of evidence was constructed for each efficacy outcome by linking treatments.
7.	Is it apparent that poor quality studies were included thereby leading to bias?	**No.** Based on the Submitter's systematic review report, Risk of bias assessment was performed using the recommendations in the NICE 'guide to the methods of technology appraisal'. The results of the quality assessment of individual trials were provided in the submitted report. All studies were assessed as being of good quality with an acceptable risk of bias (bias
8.	Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No.** There was no selective reporting of outcomes.
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**. The patient populations were broadly similar for a number of characteristics (e.g. age, post-menopausal status and performance status). However, There were differences across the studies (in terms of HR+/HER2- status, prior chemotherapy and prior endocrine therapy) that could impact comparability of the MONARCH 2 trial with other included studies.
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**. In order to show between-study similarities, the - submitted NMA report described the distribution of key baseline characteristics of the study populations along with a description of study design characteristics. Between-study heterogeneity was assessed using a qualitative comparison of study and population characteristics.
11.	Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Yes**. The indirect comparisons should be based on relative effect measures. For the binary endpoints (ORR and CBR), the model codes from the NICE technical support document 2 for binary endpoints (using a logit link) was used,[55] and the treatment effect was measured as an odds ratio. For the survival endpoints (PFS and OS), the model code in Woods 2010[56] was used, which allowed for the inclusion of binary data or median survival data where hazard ratios were not reported in the study publication
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?	**Yes.** For Loops in all networks, inconsistency was assessed using inconsistency models and compared against models assuming consistency.

Table 7.13: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis† (network meta-analysis of studies connected to MONARCH 2 – Endocrine-Resistant)		
ISPOR Questions		**Details and Comments**
13.	In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Yes.** The analyses combined combine estimates of the direct comparisons with estimates of the indirect comparisons, where closed loops existed.
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?	**Not applicable**. The inconsistency assessment showed strong evidence of inconsistency across the endpoints assessed.
15.	Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes.** Both fixed effects and random effects models were employed for each endpoint. The best fitting model was determined using the Deviance Information Criterion (DIC**).**
16.	If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Yes.**
17.	If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Yes, in part.** Where possible, sensitivity and subgroup analyses were conducted to address the heterogeneity observed. However, methods to adjust for heterogeneity (e.g., using meta-regression) were not considered to be feasible based on the limited study data available.
18.	Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes.** In the Submitter's NMA report, an evidence network was graphically presented for each efficacy outcome.
19.	Are the individual study results reported?	**Yes**. The effect estimates of all outcomes included in the NMA were provided in the submitted systematic review and NMA reports.
20.	Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**Yes.** The Submitter's original NMA report provided the pairwise direct comparisons (where available) along with indirect results for each of the competing interventions versus FUL500 as the reference treatment. During the review process, and following pCODR's request for additional information, Submitter provided a table of pairwise comparisons that showed relative effect of all treatment options included in the network meta-analyses versus abemaciclib + fulvestrant as the reference treatment.
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% CrI) were reported for estimates of effect.
22.	Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**Yes.** In the submitted report, the probabilistic ranking plots were presented for all comparators that were included in the NMA.

Table 7.13: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis† (network meta-analysis of studies connected to MONARCH 2 – Endocrine-Resistant)		
	ISPOR Questions	**Details and Comments**
23.	Is the impact of important patient characteristics on treatment effects reported?	**Yes, in part** A sensitivity analysis was performed to assess the impact of prior chemotherapy in the metastatic setting on the results of the NMA. No other assessments of heterogeneity were performed based on specific patient characteristics.
24.	Are the conclusions fair and balanced?	**Yes.** The submitted NMA concluded that combination endocrine and targeted therapy regimens ABE-FUL, PALFUL and EXE-EVE provided greater treatment benefit compared to single endocrine therapies for PFS, ORR and CBR. It was also noted in the conclusions section that the results of the NMA needed to be interpreted with caution due to the between study heterogeneity.
25.	Were there any potential conflicts of interest?	**Not reported.**
26.	If yes, were steps taken to address these?	**Not applicable.**
ALK = anaplastic large-cell lymphoma kinase; **ECOG PS**= Eastern Cooperative Oncology Group performance score; **EGFR =** epidermal growth factor receptor; **ISPOR** = International Society For Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparison; **NMA**= network meta-analysis; **NSCLC**= non-small cell lung cancer; **NSQ** = non squamous**; OS** = overall survival; **PD-L1** = programmed death-ligand1**PFS** = progression-free survival; † Adapted from Jansen, Value Health. 2014;17(2):157-73[58]		

Conclusion

The Submitter provided a systematic literature review and network meta-analysis (NMA) to estimate the relative treatment effects for abemaciclib + fulvestrant compared to alternative treatment options used in clinical practice for patients progressing on or after prior endocrine therapy within a MONARCH 2 aligned patient population. The NMA was conducted in a Bayesian framework and assessed efficacy outcomes (i.e., PFS, OS, ORR, and CBR). The analysis results showed that combination therapy with ABE-FUL, PAL-FUL and EXE-EVE provided greater treatment benefit compared to FUL500 in terms of PFS, ORR and CBR. No statistically significant differences in efficacy outcomes were found between ABE-FUL and PAL-FUL. The results of NMA should be interpreted with caution given the heterogeneity across the studies that could impact their comparability to the MONARCH 2 trial, and the fact that adjusting for heterogeneity was not feasible due to limited data. The results of NMA for OS remained uncertain owing to immature OS data for a relatively large number of the included studies, at the time of analysis.

8 COMPARISON WITH OTHER LITERATURE

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

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Breast Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on abemaciclib for advanced or metastatic breast cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. 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 Clinical Guidance Panel is comprised of three clinicians. 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

Literature Search Methods

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials November 2018, Embase 1974 to 2018 December 17, Ovid MEDLINE(R) ALL 1946 to December 17, 2018

#	Searches	Results
1	(abemaciclib* or Verzenio* or bemaciclib or ly2835219 or ly 2835219 or ly2835210 or ly 2835210 or ly2385219 or ly 2385219 or 60UAB198HK).ti,ab,ot,kf,kw,hw,nm.	780
2	1 use medall	150
3	1 use cctr	70
4	*abemaciclib/ or (abemaciclib* or Verzenio* or bemaciclib or ly2835219 or ly 2835219 or ly2835210 or ly 283521 or ly2385219 or ly 2385219).ti,ab,kw,dq.	557
5	4 use oemezd	339
6	5 not conference abstract.pt.	176
7	2 or 3 or 6	396
8	remove duplicates from 7	253
9	5 and conference abstract.pt.	163
10	limit 9 to yr="2013 -Current"	161
11	8 or 10	414
12	limit 11 to english language	392

1. **Literature search via PubMed**
   A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#2	#1 AND publisher[sb]	16
#1	5-(4-ethylpiperazin-1-ylmethyl)pyridin-2-yl)-(5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzimidazol-5-yl)pyrimidin-2-yl)amine [Supplementary Concept] OR abemaciclib*[tiab] OR Verenzio*[tiab] OR bemaciclib*[tiab] OR ly2835219[tiab] OR ly 2835219[tiab] OR ly2835210[tiab] OR ly 2835210[tiab] OR ly2385219[tiab] OR ly 2385219[tiab] OR 60UAB198HK[rn]	149

2. Cochrane Central Register of Controlled Trials (Central)
   Searched via Ovid

3. Grey Literature search via:

Clinical Trial Registries:

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

World Health Organization
http://apps.who.int/trialsearch/

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

Search: Verzenio / abemaciclib, breast cancer

Select international agencies including:

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

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

Search: Verzenio / abemaciclib, breast cancer

Conference abstracts:

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

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

Search: Verzenio / abemaciclib, breast cancer – last 5 years

Detailed Methodology

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2018Dec17) with in-process records & daily updates via Ovid; Embase (1974-2018Dec17) via Ovid; the Cochrane Central Register of Controlled Trials (November 2018) via Wiley; 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 concepts were Verzenio and abemaciclib.

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

The search is considered up to date as of April 4, 2019.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited

to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

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

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

Quality Assessment

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

Data Analysis

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

Writing of the Review Report

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

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

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