CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Palbociclib (Ibrance) with Fulvestrant for Metastatic Breast Cancer

May 3, 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 palbociclib (Ibrance) plus fulvestrant (Faslodex) for 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 palbociclib (Ibrance) plus fulvestrant (Faslodex) for 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 palbociclib (Ibrance) plus fulvestrant (Faslodex) for metastatic breast cancer, a summary of submitted Provincial Advisory Group Input on palbociclib (Ibrance) plus fulvestrant (Faslodex) for metastatic breast cancer., and a summary of submitted Registered Clinician Input on palbociclib (Ibrance) plus fulvestrant (Faslodex) for metastatic breast cancer., and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the efficacy and safety of palbociclib (Ibrance) in combination with fulvestrant for the treatment of women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2–) locally advanced breast cancer (ABC) or metastatic breast cancer (mBC) who progressed after prior endocrine therapy.

Health Canada has issued marketing authorization for use of palbociclib in combination with fulvestrant in women whose disease progressed after prior endocrine therapy. Pre- or perimenopausal women must also be treated with a luteinizing hormone releasing hormone (LHRH) agonist.

The recommended dose of palbociclib is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days. In combination with 500 mg fulvestrant by intramuscular injection on day 1 and 15 of cycle one and then on day 1 of each subsequent cycle (28 days).

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one phase III randomized controlled trial (RCT).

PALOMA-3 was a phase III, international, multicenter, randomized, double-blind, placebo-controlled trial comparing (in a 2:1 ratio) palbociclib + fulvestrant with placebo + fulvestrant in women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2–) metastatic breast cancer (mBC)whose disease had progressed after prior endocrine therapy regardless of their menopausal status.[1-3] The trial was conducted at 144 sites in 17

countries, including 11 centres in Canada. The study consisted of a pre-randomization phase, a randomization and treatment phase, and a post-treatment follow-up period.[4] A total of 521 eligible patients were randomized in a 2:1 ratio to receive palbociclib + fulvestrant (n=347) or placebo + fulvestrant (n=174) in 28-day cycles. All pre- or peri-menopausal women were also treated with a LHRH agonist at least four weeks before randomization and while on treatment.[1,5] Randomization was stratified based on three factors: sensitivity to previous hormonal therapy, menopausal status at the baseline, and presence of visceral metastases.

The primary endpoint of the study was investigator-assessed progression-free survival (PFS), defined as the time from randomization to disease progression or death.[2] Key secondary efficacy endpoints included overall survival (OS), objective response rate (ORR), duration of response, clinical benefit, and safety.[1,2,6] Patient-reported outcomes (PRO) were also measured and reported.[2,4,7]

The median age of the study participants was 57 years (range 29 to 88), with the majority of patients being younger than 65 years of age (75.2%), White (73.9%), or from non-Hispanic or non-Latino ethnicities (94.0%). A total of 77.9% of the patients had measurable disease, with the most commonly involved disease sites being bone (75.2%), liver (39.9%), and lymph nodes (38.6%). A larger proportion of patients in the palbociclib + fulvestrant arm had an ECOG performance score of 1 (40.3% versus 33.9% in the placebo + fulvestrant arm).[2,5]

Data from the PALOMA-3 trial were analysed on the following data cut-off dates:

Data cut-off date	Analysis	Median duration of follow up	Number of observed events (N=521)	Reference
05-Dec-2014	Pre-planned interim analysis of the primary endpoint (PFS) and safety data	5.6 months	195 PFS events	Turner, 2015[2]
16-Mar-2015	1st updated analysis of PFS	8.9 months	259 PFS events	Cristofanilli, 2016[1]
23-Oct-2015	2nd updated analysis : final PFS analysis and a formal interim analysis of OS	15.8 months for palbociclib + fulvestrant & 15.3 months for placebo + fulvestrant	333 PFS events	Turner, 2017.[8] Checkpoint responses[9]
13-Apr-2018	Pre-planned final analyses of OS and safety data	44.8 months	310 deaths	Turner, 2018[3]

Efficacy

The key efficacy outcomes of the PALOMA-3 trial are presented in Table 1.1.

Progression-free survival (PFS)

As of the 05-December-2014 data cut-off date, 102 PFS events (29.3%) had occurred in the palbociclib + fulvestrant arm and 93 events (53.4%) in the placebo + fulvestrant arm. The median PFS was 9.2 months (95% CI, 7.5, not estimable) with palbociclib + fulvestrant and 3.8 months (95% CI 3.5, 5.5) with placebo + fulvestrant (HR= 0.42; 95% CI 0.32, 0.56; p <0. 001).[2,5] The results of this analysis crossed the pre-specified Haybittle-Peto efficacy boundary of α=0.00135; therefore, the study was stopped early (in April 2015) for efficacy (i.e., statistically significant prolongation in PFS).[1] As shown in Table 1.1, the results of the blinded audit, conducted on a random sample of approximately 40% of patients, were consistent with the results of the primary (interim) analysis.[2,5]

As of the October-2015 data cut-off, 200 events (57.6%) had occurred in the palbociclib + fulvestrant arm and 133 events (76.4%) in the placebo + fulvestrant arm. The median PFS was 11.2 months (95% CI 9.5, 12.9) with palbociclib + fulvestrant versus 4.6 months (95% CI 3.5, 5.6) with placebo + fulvestrant (HR = 0.497; 95% CI 0.398, 0.620]; p<0.0001).[8]

Overall survival (OS)

The final analysis OS data was conducted after the data reached a 60% maturity (i.e., 310 deaths among 521 patients). At the data-cut-off date, 201 deaths had occurred in the palbociclib + fulvestrant arm and 109 deaths in the placebo + fulvestrant arm. The median OS was 34.9 months (95% CI 28.8, 40.0) for patients in the palbociclib + fulvestrant arm and 28.0 months (95% CI 23.6, 34.6) for those in the placebo + fulvestrant arm (stratified HR= 0.81; 95% CI, 0.64, 1.03; P = 0.09).[3] The OS rate at 3 years was 50% (95% CI 44%, 55%) in the palbociclib + fulvestrant arm and 41% (95% CI 33%, 48%) in the placebo + fulvestrant arm.[3]

Objective Response Rate (ORR)

At the time of the preplanned interim analysis (05-December-2014), ORR was 10.4% (95% CI 7.4, 14.1) in the palbociclib + fulvestrant arm and 6.3% (95% CI 3.2, 11.0) in the placebo + fulvestrant arm (P = 0.16).[2]

At the 16-March-2015 data cut-off date, ORR was estimated to be statistically higher in the palbociclib + fulvestrant arm (19%; 95% CI 15.0%, 23.6%) than in the placebo + fulvestrant arm (9%; 95% CI 4.9%, 13.8%; p=0.0019).[1] For patients with measurable disease at baseline, ORR was 24.6% (95% CI 19.6%, 30.2%) in the palbociclib + fulvestrant arm and 10.9% (95% CI 6.2%, 17.3%) in the placebo + fulvestrant arm. (p=0.0012).[1]

Clinical Benefit Rate (CBR)

As of the 05-December-2014 data cut-off date, CBR was estimated to be statistically higher in the palbociclib + fulvestrant arm (34.0%; 95% CI 29.0, 39.3) than in the placebo + fulvestrant arm (19.0%; 95% CI 13.4, 25.6; P<0.001).[2]

At the time of the first updated analysis (16-March-2015), the CBR was 67% (95% CI 61.3%, 71.5%) in the palbociclib + fulvestrant arm and 40% (95% CI 32.3, 47.3) in the placebo + fulvestrant arm.[1] For patients with measurable disease at baseline, CBR was estimated to be 64% (95% CI 57.7%, 69.6%) in the palbociclib + fulvestrant arm and 36% (95% CI 28.2%, 44.8%) in the placebo + fulvestrant arm (p<0.0001).[1]

Duration of Response (DOR)
At the time of the second updated analysis (23-October-2015), DOR was 10.4 months (95% CI 8.3, not estimable) in the palbociclib + fulvestrant arm and 9.0 months (95% CI 5.6, not estimable) in the placebo + fulvestrant arm.[9]

Quality of Life (QoL)

From baseline to cycle 14, questionnaire completion rates (completion of ≥1 question) were ≥95.8% for the EORTC QLQ-C30, and ≥93.8% the EORTC QLQ-BR23 questionnaires.[7]

As shown in Table 1.1, the mean baseline scores for global QoL were similar between the palbociclib + fulvestrant (65.9; 95% CI 63.5, 68.2) and placebo + fulvestrant arms (65.3; 95% CI 61.9, 68.6). However, while receiving study treatments, the global QoL score was significantly higher in the palbociclib + fulvestrant arm (66.1; 95% CI 64.5, 67.7) than in the placebo + fulvestrant arm (63.0; 95% CI 60.6, 65.3; P = 0.0313). No significant differences were observed for other QLQ-BR23 functioning domains, breast or arm symptoms. In addition, treatment with palbociclib + fulvestrant resulted in a statistically significant delay in deterioration of QoL (HR = 0.641; 95% CI 0.451, 0.910; P = 0.0065), and pain (HR = 0.642; 95% CI 0.487–0.846; p<0.001).[7]

Harms

A summary of safety data from the PALOMA-3 primary analysis is presented in Table 1.1. More details are provided in section 6.3.2.2.

As of the 05-December-2014 data cut-off date, 97.7% of patients in the palbociclib + fulvestrant arm and 89.0% of those in the placebo + fulvestrant arm had at least one reported AE (any grade) The most common (adverse events (AEs) with palbociclib + fulvestrant group included neutropenia, leukopenia, fatigue, nausea, anemia, and thrombocytopenia. Grade 3 or 4 AEs occurred in 69.3% of patients in the palbociclib + fulvestrant arm and 18.0% of those in the placebo + fulvestrant arm. The most common grade 3 or 4 AEs reported with palbociclib + fulvestrant included: neutropenia, leukopenia, anemia, and thrombocytopenia.[2] Serious AEs (any cause) occurred in 9.6% of the patients in the palbociclib +fulvestrant arm and 14.0% of the patients in the placebo + fulvestrant arm. Discontinuation of palbociclib (or matching placebo) due to AEs was reported in 2.6% of patients receiving palbociclib + fulvestrant and 1.7% of those receiving placebo + fulvestrant.[2]

The results of the long-term safety analysis (03-April-2018 data cut-off date) were consistent with those in those of the interim analysis, with neutropenia, infections, leukopenia, fatigue, nausea, and anemia being the most commonly reported AEs.[3] The most common grade 3 or 4 AEs reported with palbociclib + fulvestrant were neutropenia, and leukopenia.[3] As of the 03-April-2018, 5.5% of patients in the palbociclib + fulvestrant arm and 3.4% of those in the placebo + fulvestrant arm discontinued the study treatment due to AEs.[3]

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

	PALOMA-3	
Primary Outcome	**palbociclib + fulvestrant (n=347)**	**placebo + fulvestrant (n=174)**
PFS		
Primary analysis(by Investigator)†		
Events (%)	102 (29.4)	93 (53.4)
Median, months (95% CI)	9.2 (7.5, NE)	3.8 (3.5, 5.5)
HR (95% CI)	0.42 (0.32, 0.56)	
p-value	<0. 001	
Primary analysis(by BICR)†		
Median, months (95% CI)	NE (NE,NE)	3.7 (3.4, 7.2)
HR (95% CI)	0.27 (0.16, 0.46)	
p-value	<0.001	
Final analysis††		
Median, months (95% CI)	11.2 (9.5, 12.9)	4.6 (3.5, 5.6)
HR (95% CI)	0.50 (0.40, 0.62)	
p-value	<0.0001	
Key Secondary Outcomes		
OS‡		
Events (%)	201 (57.9)	109 (62.6)
Median, months (95% CI)	34.9 (28.8, 40.0)	28.0 (23.6, 34.6)
HR (95% CI)	0.81 (0.64, 1.03)	
p-value	0.09	
OS rate, % (95% CI)		
at 3 years	50 (44, 55)	41 (33, 48)
ORR		
Primary analysis†, % (95% CI)	10.4 (7.4, 14.1)	6.3 (3.2, 11.0)
p-value	0.16	
1st updated analysis§, % (95% CI)	19.0 (15.5, 23.6)	9.0 (4.9, 13.8)

Table 1.1: Highlights of Key Outcomes in the PALOMA-3 trial			
		PALOMA-3	
p-value		0.0019	
CBR			
Primary analysis†, % (95% CI)	34.0 (29.0, 39.3)		19.0 (13.4, 25.6)
p-value		<0.001	
1st updated analysis§, % (95% CI)	67.0 (61.3, 71.5)		40.0 (32.3, 47.3)
p-value		<0.0001	
Duration of objective response, months			
1st updated analysis§, median (95% CI)	9.3 (NR, NR)		7.6 (NR, NR)
		<0.001	
2nd updated analysis††, % (95% CI)	10.4 (8.3, NE)		9.0 (5.6, NE)
p-value		<0.0001	
HrQoL			
Global QoL			
Mean scores at baseline	65.9 (63.5, 68.2)		65.3 (61.9, 68.6)
Mean scores at the data cut-off	66.1 (64.5, 67.7)		63.0 (60.6, 65.3)
p-value		0.0313	
Median TTD in QoL, months (95% CI)	NE (NE, NE)		NE (5.7, NE)
HR (95% CI)		0.641 (0.451, 0.910)	
p-value		0.0065	
Median TTD in Pain, months (95% CI)	8.0 (5.6, NE)		2.8 (2.3, 5.4)
HR (95% CI)		0.642 (0.487, 0.846)	
p-value		<0.001	
Safety Outcomes†, n (%)	**palbociclib + fulvestrant (n=345)**		**placebo + fulvestrant (n=172)**
AEs any grade	337 (97.7)		153(89.0)
Grade ≥3 AEs	239 (69.3)		31 (18.0)
SAEs any grade	NR (9.6)		NR (14.0)
WDAE	9 (2.6)		3 (1.7)
Withdrawal due to death	0 (0)		1 (0.6)

AE= adverse event; BICR = blinded independent central review; CBR = clinical benefit rate; CI = confidence interval; HR = hazard ratio, HRQoL = health-related quality of life, NE = not estimable; NR = not reported; ORR = objective response rate; SAE = serious adverse event; TTD = time to deterioration; WDAE = withdrawal due to adverse event

† 05-Dec-2014 data cut-off date
†† 23-Oct-2015 data cut-off date
‡ 13-Apr-2018 data cut-off date
§ 16-Mar-2015 data cut-off date

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

Patient input regarding palbociclib (Ibrance) use in combination with fulvestrant for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer was provided by two patient advocacy groups: Rethink Breast Cancer (RBC) and the Canadian Breast Cancer Network (CBCN). Their methods and input are summarized below.

From a patient perspective, metastatic breast cancer is severely debilitating and associated with pain, fatigue, and impaired ability to perform regular life activities such as working, driving and spending time with family and friends. Diagnosis of metastatic breast cancer was generally detrimental to the mental health of patients and to their finances. According to patients, current therapeutic options cause a number of side effects, fatigue being the most difficult to tolerate. Financial challenges due to treatment were identified as a major issue. Patients with a diagnosis of metastatic breast cancer understand the limitations and toxicities of current treatment options and seek to obtain the best quality of life that can be achieved in the time that is available.

Patients who had experience with the drug combination under review had a favourable outlook on the therapy. Overall, patients felt that the treatment led to a modest improvement in quality of life and a substantial improvement in disease control. Toxicity was noticeably milder and more tolerable than with other options.

Patient goals, values and expectations were centred on better progression-free survival and a sustained quality of life. Side effects were not a major consideration to patients and some measure of toxicity was deemed acceptable so long as disease control was achieved.

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.

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:

- Fulvestrant is not publically funded in any provinces for metastatic breast cancer
- Monthly monitoring and bloodwork for neutropenia with palbociclib as well as treatment visits for fulvestrant

Economic factors:

- Large number of patients eligible for treatment
- Potential for drug wastage due to dose adjustments

Registered Clinician Input

Four inputs from clinicians were received by pCODR: a submission from BC Cancer providing the perspective of a single oncologist, a joint submission from Cancer Care Ontario capturing the perspective of four clinicians (three oncologists and one oncology pharmacist), a joint submission from Alberta Health Services representing three oncologists, and one individual input from an oncologist at the Ottawa Hospital Cancer Centre, for a total of nine clinicians providing input.

The clinicians who provided input noted that there are limited treatment options for patients with metastatic hormone receptor (HR) positive, HER2-negative breast cancer who have progressed on previous endocrine therapy. These patients represent a large population and continued treatment with alternate endocrine and other non-chemotherapeutic approaches is generally preferred by clinicians. Clinicians consider palbociclib plus fulvestrant to be a safe and effective line of therapy for patients who have developed resistance to endocrine therapy including aromatase inhibitors. This combination would naturally replace second line aromatase inhibitors. Clinicians value the potential choice of using palbociclib in either the first or second line setting.

Summary of Supplemental Questions

Summary and critical appraisal of the systematic review and network meta-analysis comparing palbociclib with other therapies for HR+/HER2- Advanced or metastatic breast cancer patients whose disease progressed after prior endocrine therapy

Given the absence of head-to-head trials against other currently funded therapies in Canada, the submitter provided an indirect treatment comparison (ITC) report comparing the efficacy of palbociclib with endocrine therapies in the second line treatment of patients with HR+/HER2– locally advanced or metastatic breast cancer.[10] The submitted ITC was performed through conducting a systematic literature review and a Bayesian network meta-analysis (NMA). Key outcomes of interest were PFS/time to progression (TTP) and OS.

Results of the submitted NMA showed that palbociclib + fulvestrant was associated with a superior PFS/TTP compared with endocrine monotherapies, and no difference compared with everolimus + exemestane for the treatment of patients with HR+/HER2- locally advanced or metastatic breast cancer who progressed after prior endocrine therapy. A trend towards improvement in OS was observed when the palbociclib + fulvestrant combination was indirectly compared with other endocrine therapies. However, OS differences were not statistically significant based on the overlapping 95% credible intervals (CrIs).

Although alignment of these findings with direct evidence lends credibility to the analysis, these results should be interpreted with attention to the limitations that arise from the lack of closed loops in the network, large number of single-study connections in the network, and lack of indirect comparisons for safety data, other efficacy outcomes (objective response rate, etc.), and patient-reported outcomes.

See section 7.1 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 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for palbociclib plus fulvestrant

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="6">Population</td><td>ECOG performance score</td><td>The PALOMA-3 trial limited eligibility to patients with an ECOG performance status of 0-1. Patients with an ECOG of 2 or greater were excluded.
<table><tr><th>ECOG</th><th>Palbociclib + fulvestrant (n=347)</th><th>Placebo + fulvestrant (n=174)</th></tr><tr><td>0</td><td>207 (60%)</td><td>115 (66%)</td></tr><tr><td>1</td><td>140 (40%)</td><td>59 (34%)</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>Based on the likelihood of a worse benefit/toxicity ratio with palbociclib plus fulvestrant, the CGP does not support treatment of patients with ECOG PS greater than 1.</td></tr>
<tr><td>Age</td><td>Around 2/3 of the PALOMA-3 study participants were younger than 65 years old.
<table><tr><th>Age Group</th><th>Palbociclib + fulvestrant (n=347)</th><th>Placebo + fulvestrant (n=174)</th></tr><tr><td>≥17-<65</td><td>261 (75.2)</td><td>131 (75.3)</td></tr><tr><td>≥65- <75</td><td>86 (24.8)</td><td>43 (24.7)</td></tr></table></td><td>Do the trial results apply to all adult patients?</td><td>The CGP noted that the tolerability of palbociclib plus fulvestrant has not been sufficiently assessed in frail elderly patients.</td></tr>
<tr><td>Gender</td><td>All of the PALOMA-3 study participants were female.</td><td>Do the trial results apply to male patients?</td><td>The CGP agree that expanding the treatment indications to include the rare male patient with mBC, would be reasonable.</td></tr>
<tr><td>Visceral metastases</td><td>Patients with extensive symptomatic visceral metastases were excluded from the PALOMA-3 trial.</td><td>Are the trial results generalizable to patients with extensive symptomatic visceral metastases?</td><td>Based on the likelihood of a worse benefit/toxicity ratio with palbociclib plus fulvestrant, the CGP does not support treatment of patients with rapidly progressive visceral.</td></tr>
<tr><td>CNS metastases</td><td>Patients with uncontrolled CNS metastases were excluded from the PALOMA-3 trial.</td><td>Are the trial results generalizable to patients with uncontrolled CNS metastases?</td><td>Based on the likelihood of a worse benefit/toxicity ratio with palbociclib plus fulvestrant, the CGP does not</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				support treatment of patients with CNS metastases.
	Prior therapies	PALOMA-3 excluded patients who previously received CDK inhibitors.	Do the trial results apply to patients with a history of CDK-inhibitor therapy?	The CGP support that palbociclib + fulvestrant use should be restricted to patients who have only received 1 prior line of chemotherapy for mBC, as permitted in the PALOMA-3 trial. The CGP agreed there is no good evidence to suggest that patients receiving palbociclib with an AI as first-line treatment, who develop disease progression, would benefit from substituting the AI with fulvestrant and continuing palbociclib. The CGP therefore agreed that the results of the PALOMA-3 trial cannot be extended to patients who have received a CDK-inhibitor in prior lines of treatment.
Intervention	Dosing schedule	In the PALOMA-3 trial, palbociclib was administered orally in 28-day cycles: 125 mg once daily day for 21 days, followed by a 7-day treatment-free interval + fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and every 28 days thereafter starting from Day 1 of Cycle 1	Are there other dosing schedules used in Canada for the treatment of adult women with HR+/HER2 negative locally ABC or mBC in 2nd and greater lines of therapy setting)? If so, are the trial results applicable to the Canadian practice?	The CGP agreed that the trial dosing schedule of palbociclib and fulvestrant are generalizable to the Canadian setting.
	Line of therapy	The PALOMA-3 trial limited eligibility to patients who progressed during or after previous endocrine therapy for advanced or metastatic breast cancer (2nd and greater lines of therapy).	Do the trial results apply to the first-line treatment of advanced or metastatic breast cancer?	The CGP agreed that the results of the PALOMA-3 trial cannot be generalized to the first line setting (switching letrozole for fulvestrant).
Comparator	Standard of care	The comparator in the PALOMA-3 trial was fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and every 28 days thereafter starting from Day 1 of Cycle 1.	Are the findings of the PALOMA-3 trial generalizable to patients who may receive	The CGP agreed that fulvestrant (with placebo) is not currently funded in most Canadian provinces and is not widely used. However, the NMA did provide

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		Plus placebo matching with palbociclib in the intervention arm (in terms of schedule and route of administration). The review team identified chemotherapy agents and other endocrine therapy options, including aromatase inhibitors and selective estrogen receptor modulators as potentially relevant comparators. The submitter provided an ITC that included indirect comparisons of palbociclib + everolimus with other available endocrine-based treatment options currently approved in Canada for the patients group of interest in this review. Please refer to the Method lead ITC assessment section 7 for more information.	chemotherapy or other endocrine therapies instead of fulvestrant?	comparisons with other commonly used endocrine therapies. PFS/TTP were superior for palbociclib + fulvestrant compared with endocrine monotherapies, but similar to the combination of everolimus + exemestane.
Outcomes	Appropriateness of primary and secondary outcomes	Primary outcome: PFS Secondary outcomes: OS, ORR, Duration of response, clinical benefit rate, quality of life, and safety	Were the primary and secondary outcomes appropriate for the trial design?	The CGP agrees that PFS is a reasonable outcome in breast cancer.
Setting	Countries participating in the trial	The PALOMA-3 trial was conducted in 144 centres in Canada (11 centres), US, Belgium, Germany, Ireland, Italy, Netherlands, Portugal, Romania, Russian Federation, Turkey, Ukraine, UK, Australia, Japan, Republic of Korea, and Taiwan. Fourteen percent of patients were recruited from Canada (29/347 [8%] in the palbociclib + fulvestrant arm and 10/174 [6%] in the placebo + fulvestrant arm).	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)?	It is unlikely that practice patterns in the participating countries are sufficiently different to affect the generalizability of outcomes to the Canadian setting.

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; **UK** = the United Kingdom; **US** = the United States of America

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. 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.

Need

With the development of targeted agents, and a pCODR recommendation (2016) and subsequent provincial reimbursement of the combination palbociclib/letrozole, an estimated 50-60% of women presenting with mBC from 2017 onwards may have received palbociclib in combination with letrozole first-line, and will not be eligible for palbociclib + fulvestrant. Thus, in the postmenopausal population, palbociclib + fulvestrant is most likely to be given to a limited number of patients who were not eligible for a variety of reasons to receive first-line palbociclib/letrozole (eg. received non-steroidal AI treatment for mBC before palbociclib was available, chose not to receive it, or had a contraindication to palbociclib that is no longer operative). The main competing alternative second-line hormonal treatments would therefore be exemestane with/without everolimus, tamoxifen or single agent fulvestrant. In Canada, this option is only available to patients with private insurance, or those who are willing to pay for the treatment. Patients previously treated with tamoxifen, who remain premenopausal would be good candidates for palbociclib + fulvestrant provided they are able to undergo ovarian suppression/ablation.

Patient input, through Rethink Breast Cancer and Canadian Breast Cancer Network advocacy groups, confirms an ongoing need for new therapies that can control mBC and maintain quality of life. Between the 2 groups, a total of 26 patients had experience with palbociclib + fulvestrant, and almost all reported benefit in terms of disease control and/or improvement in quality of life, and would recommend this treatment to other patients.

A total of 9 Registered Clinicians from Cancer Agencies in three provinces (Ontario, BC and Alberta) provided input. Overall, they are favorably impressed with the results of the PALOMA-3 trial, both in terms of efficacy of palbociclib + fulvestrant, as well as low toxicity and improved quality of life. They mention that there are limited treatment

options for patients with HR+/HER2 negative mBC, whose disease has progressed on previous endocrine therapy, and who wish to delay or avoid chemotherapy. Patients in this category are common, and continued treatment with alternate endocrine and other non-chemotherapeutic approaches is generally preferred by oncologists. Clinicians consider palbociclib + fulvestrant to be a safe and effective next line therapy for patients whose tumors have developed resistance to endocrine therapy including aromatase inhibitors, and they are encouraged by the low toxicity especially in comparison to an alternative treatment incorporating another targeted agent, everolimus with exemestane. For premenopausal women willing to undergo ovarian ablation/suppression this treatment provides an alternative to tamoxifen, which has limited efficacy in the second line setting. It provides access to palbociclib for this group which is currently excluded from palbociclib funding in the first line setting. Clinicians also value the potential choice of using palbociclib in either first or second line settings. The Provincial Advisory Group input focused on concerns that fulvestrant is not publically funded in any provinces for use in mBC, leading to extra costs for drugs and administration, and also on the other extra costs related to increased level of monitoring for patients on palbociclib, and possible drug wastage. Questions were raised about the appropriateness of using palbociclib + fulvestrant in patient groups not included in PALOMA-3 (males, those with extensive visceral or uncontrolled CNS metastases, ECOG PS 2 or greater, HER2 double equivocal). If this therapy is approved, PAG raised practical questions about timing in relation to other therapies.

Effectiveness

PALOMA-3 was a phase III, international, multicentre, randomized double-blind placebo controlled trial that evaluate the efficacy and safety of palbociclib + fulvestrant in women with HR+/HER2 negative mBC whose disease had progressed after prior endocrine therapy. Previous chemotherapy was permitted, but only 1 line of treatment for mBC. The trial was conducted between September 2013 and August 2014 in 144 sites in 17 countries, including 11 in Canada. Eligible patients, age 18 years or older, were randomized in a 2:1 ratio to receive palbociclib 125 mg orally daily, 3 weeks on/1 week off, in 28 day cycles versus an oral placebo. All patients received fulvestrant 500 mg IM d1 and d15, then every 28 days. Treatment was continued until progression of disease, intolerance or patient withdrawal. Patients could continue treatment beyond the time of RECIST-defined disease progression at the discretion of the investigator if that was considered to be in the best interest of the patient and as long as no new anticancer treatment was initiated. All pre/perimenopausal women were also treated with an LHRH agonist starting 4 weeks before randomization. Post-baseline tumor assessments (using CT, MRI or both) were performed every 8 weeks in the first year, and every 12 weeks thereafter until clinical or radiological disease progression according to RECIST criteria. The primary endpoint was PFS, with secondary endpoints of OS, overall response rate (ORR), clinical benefit response (CBR) and duration of response (DOR). Safety endpoints were toxicity and QOL.

A total of 521 women were randomized, 39 (14%) from Canada, with 347 in the palbociclib + fulvestrant arm and 174 in the placebo + fulvestrant arm. Median age was 56.9 years, with predominantly white participants (73.9%) and measurable disease present in 77.9% of cases, the remainder having partially-lytic bone only disease. ECOG PS values were 0 in 61.8 % and 1 in 38.2%. The most commonly involved disease sites were bone (75.2%), liver (39.9%) and lymph nodes (38.6%). Stratification factors were well balanced between the palbociclib versus placebo arms respectively, with 79.3% vs 79.2% being postmenopausal, 79.0% vs 78.2% having documented sensitivity to prior hormonal therapy and 59.4% vs 60.3% having visceral metastases. Also, in general, baseline characteristics were well-balanced between arms, except that a larger proportion of women receiving palbociclib

versus placebo had PS 1 (40.3% vs 33.9%) and had received more than 1 prior hormonal regimen (61.7% vs 55.7%). Chemotherapy was given in 72.3% vs 79.3% of cases, with 41.5% vs 43.1% receiving (neo)adjuvant therapy only and 30.8% vs 36.2% receiving chemotherapy for mBC (some of whom also received adjuvant chemotherapy).

At the time of pre-planned interim analysis (5 December 2014 cut-off), after a median follow up duration of 5.6 months, 102 (29.3%) PFS events had occurred in the palbociclib + fulvestrant arm and 93 (53.4%) events in the placebo + fulvestrant arm. Median PFS rates were 9.2 months (95% CI 7.5, not estimable) versus 3.8 months (95% CI 3.5, 5.5) respectively (HR=0.42, 95% CI 0.32, 0.56; p<0.001) [Turner 2015]. The results crossed the pre-specified efficacy boundary and the study was stopped early (in April 2015) but after full patient enrollment.[1] The results of a Blinded Central Independent Review (BCIR) of PFS, conducted on a random sample of approximately 40% of cases, were consistent with those of the Investigator Assessment interim analysis, with median PFS not estimable for palbociclib and 3.7 months (95% CI 3.4, 7.3) for placebo arms respectively (HR=0.27, 95% CI 0.16, 0.46; p<0.001). At the time of an exploratory updated analysis (16 March 2015 cut-off), with a median follow up duration of 8.9 months, 145 (41.8%) PFS events had occurred in the palbociclib arm and 114 (65.5%) events in the placebo arm.[1] Median PFS rates were 9.5 months in palbociclib arm versus 4.6 months in placebo arm (HR=0.46, 95% CI 0.36, 0.49; p<0.0001). Subgroup analysis showed similar levels of benefit across stratification factors (menopausal status, sensitivity to prior hormone therapy, presence of visceral metastases) and for many baseline demographic factors, except for those with a >24 months DFI, women who had received 3 or more lines of previous anti-cancer therapy for mBC and non-white ethnic groups, for which there was no apparent benefit. The study was not powered to detect PFS benefit in the sub-groups, and these analyses are considered exploratory.

More mature OS data were analyzed after a median follow up of 44.8 months (13 April 2018 cut-off), with 201 deaths in the palbociclib arm and 109 deaths in the placebo arm. Median OS was 34.9 months (95% CI 28.8, 40.0) for palbociliclib + fulvestrant versus 28.0 months (95% CI 23.6, 34.6) for placebo + fulvestrant (stratified HR=0.81, 95% CI 0.64, 1.03; p=0.09). Similar trends for benefit were seen in other secondary endpoints of ORR, CBR, DOR (see Section 6.1.2.2).

A critical appraisal of the Network Meta-Analysis (NMA) submitted by the Manufacturer confirmed that palbociclib + fulvestrant was associated with superior PFS/TTP compared with endocrine monotherapies, and no difference compared with everolimus + exemestane, for treatment of women with HR+/HER2 normal mBC whose disease had progressed after prior endocrine therapy. While no difference was found in PFS between palbociclib + fulvestrant compared with everolimus plus exemestane, the results should be interpreted with caution due to the limitations. A trend for improved OS was observed when palbociclib + fulvestrant was indirectly compared with all other endocrine therapies. The CGP agreed with the Methods team that it was reasonable to exclude chemotherapy regimens from the NMA, as usual clinical practice is to try all possible endocrine options before considering chemotherapy, unless there is clear evidence of complete endocrine resistance, or the presence of rapidly progressive/life-threatening disease.

Safety

A total of 3 safety analyses were performed, at times of first interim and updated PFS analyses and at the time of OS analysis (see Section 6.1.2.2). The results were broadly similar, so those for the final analysis (cut-off date 13 April 2018) after a median follow up of 44.8 months are presented here.[14] The median number of cycles delivered was 12 (IQR 4, 21) in the palbociclib + fulvestrant arm and 5 (IQR 2, 12) in the placebo + fulvestrant

arm. Respective rates of the commonest grade 3/4 AEs were neutropenia (69.6% vs 0%), leukopenia (38.3% vs 5.8%), although febrile neutropenia was uncommon (1% vs 0%). Lesser grades of toxicities such as fatigue and nausea were commoner in the palbociclib arm.

Patient Reported Outcomes (PROs) were evaluated in a subset (approximately 75%) of the population, who completed baseline and at least 1 post-baseline PRO assessments.[7] Using EORTC QLQ-C30 and its breast cancer module (EORTC QLQ-BR-23) and EQ-5D scales, change from baseline in global QOL was significantly greater (p=0.031) in the palbociclib arm (66.1; 95% CI 64.5, 67.7) compared with the placebo arm (63.0; 95% CI 60.6, 65.3) and deterioration was significantly delayed (HR=0.641, 95% CI 0.45, 0.91; p=0.0065). Similarly, patients in the palbociclib arm experienced statistically significant (p=0.0011) reductions in pain from baseline of -3.3 (95% CI -5.1, -1.5) vs 2.0 (95% CI -0.6, 4.6), and significantly less (p=0.0369) deterioration in nausea/vomiting of 1.7 (95% CI 0.4, 3.0) vs 4.2 (95% CI 2.3, 6.1). More detailed results are given in Section 6.1.2.2.)

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit of palbociclib + fulvestrant, compared with fulvestrant, in the treatment of women with HR+/HER2 negative mBC whose disease has progressed after prior endocrine therapy, based on the results of one high-quality randomized placebo-controlled trial that, at interim analysis after a median follow up of 5.6 months, demonstrated a clinically meaningful and statistically significant benefit in PFS (HR=0.42, p=0.001). The PFS results were confirmed by blinded independent audit (BICR) of 40% of patients selected by a third party, and supported by an exploratory analysis of PFS after a median follow up of 8.9 months, which showed a 5 month difference between the two arms in favor of palbociclib (HR=0.46, p<0.0001). At final analysis after a median follow up of 44.8 months, there was also a trend (HR=0.81, p=0.09) for benefit in the secondary endpoint of OS, with a 6 month difference in favor of palbociclib. Adverse event profiles favored the palbociclib + fulvestrant arm, as did PROs.

The CGP also considered a number of factors influencing this conclusion:

- The comparison regimen, fulvestrant (with placebo) is not currently funded in most Canadian provinces and is not widely used. However, a NMA considered to be methodologically sound, did provide comparisons with other commonly used endocrine therapies. PFS/TTP were superior for palbociclib + fulvestrant compared with endocrine monotherapies, but similar to the combination of everolimus + exemestane.
- Although through indirect comparison between palbociclib + fulvestrant versus everolimus + exemestane in the NMA it was not possible to determine a difference in efficacy based on PFS/OS, registered clinician input suggests that the side-effect profile of the former regimen is more favorable. Everolimus + exemestane is often poorly tolerated due to mucositis, nausea, diarrhea and rash. Thus, the CGP considered that there is net clinical benefit for palbociclib + fulvestrant, and this regimen may be preferred by treating clinicians.
- While there was no direct or indirect comparison of palbociclib plus fulvestrant with tamoxifen, the CGP felt confident that there was sufficient body evidence to confirm that AI's are more effective than tamoxifen. The CGP therefore agreed that as the PALOMA-3 results were consistent with the palbociclib combination having improved efficacy in comparison to aromatase inhibitors that are known to be more effective than tamoxifen, palbociclib + fulvestrant is likely to have superior efficacy to tamoxifen monotherapy, and may be the preferred option.
- The trial was stopped early for efficacy benefit (although after full recruitment) and this could lead to a substantial over-estimate of benefit in a trial with fewer than 500 PFS or OS events.

- In their report of the results of the long-term OS analysis, the investigators noted that it is challenging to find a threshold for significant prolongation of OS in the context of a disease in which survival after disease progression is substantially longer than the duration of the trial. The authors suggested that in order to detect a significant improvement in OS (HR=0.80), an 80% power calculation would involve more than 700 events, as compared to the PALOMA-3 trial that achieved approximately 46% power to detect a HR=0.80, with 310 deaths among 521 patients at the time of the OS analysis.
- In the PALOMA-3 trial, patients could continue treatment beyond the time of RECIST-defined disease progression at the discretion of the investigator if that was considered to be in the best interest of the patient. It would be reasonable to allow this in the clinical setting provided follow up radiological assessments at 8 weekly intervals (as required in the trial) do not show ongoing progressive disease.
- If this treatment is approved, questions arise (as articulated by PAG) about its potential use in subgroups of patients not included in the PALOMA-3 trial. Because of the likelihood of a worse benefit/toxicity ratio, CGP does not support treatment of patients with ECOG PS greater than 1, and those with rapidly progressive visceral or uncontrolled CNS metastases. However, expanding the treatment indications to include the rare male patient with mBC, and those who have HER2 double-equivocal tumors would be reasonable.
- The CGP recommends that palbociclib + fulvestrant use should be restricted to patients who have only received 1 prior line of chemotherapy for mBC, as permitted in the PALOMA-3 trial.
- There is no good evidence to suggest that patients receiving palbociclib with an AI as first-line treatment, who develop disease progression, would benefit from substituting the AI with fulvestrant and continuing palbociclib. Furthermore, if patients have already received another CDK 4/6 inhibitor, such as ribociclib, they would not be appropriate candidates for treatment with palbociclib + fulvestrant.
- For patients with mBC who recently started fulvestrant as a second-line endocrine therapy and have no evidence of disease progression, it would be reasonable to allow the addition of palbociclib if recommended by the treating clinician.
- There is no good evidence to support the use of palbociclib + fulvestrant for patients whose disease is progressing on everolimus + exemestane, as this represents a third-line endocrine manipulation, and is outside the scope of the PALOMA-3 trial.
- While outside of the scope of this review, it is the opinion of the CGP to not recommend the use of palbociclib + fulvestrant as a first-line endocrine treatment for mBC. For postmenopausal women, the option of palbociclib + letrozole is available and funded as first-line therapy. It is conceivable that palbociclib + fulvestrant, with an LHRH agonist, would be a more effective first-line endocrine treatment than single agent tamoxifen for peri/premenopausal women, but this was not tested in the PALOMA-3 study. If palbociclib + fulvestrant is available as a second-line option, there is unlikely to be detrimental effect for these patients.
- The CGP deemed it to be beyond the scope of their review to make firm recommendations for further treatment of patients developing progressive disease on palbociclib + fulvestrant. However, if palbociclib + fulvestrant is endorsed as second-line endocrine treatment for mBC, under current provincial funding guidelines the use of any CDK 4/6 inhibitors and everolimus as third-line agents would be precluded. It is most likely that clinicians would chose to use available chemotherapy regimens in this setting.
- Many Canadian clinicians will already have experience in the use of palbociclib, with letrozole, in the first-line treatment of mBC, and most cancer centres will have processes in place for the appropriate safety monitoring of palbociclib treatment. Administration of fulvestrant requires loading doses and monthly IM injections, which can be uncomfortable for patients and will be associated with extra costs. There are similar issues related to the delivery of LHRH agonist injections for pre/perimenopausal women.

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 cancer in Canadian women. In 2017, an estimated 26,300 women were diagnosed with breast cancer and an estimated 5,000 women died of this disease.[11] Although most women diagnosed will be discovered at an early stage of disease, some will progress to an advanced or incurable state despite optimal therapy. A minority of women, 5-10%, will present with locally advanced or metastatic disease at diagnosis. Metastatic breast cancer is considered incurable, but treatable, with 70% of women dying of their disease within 5 years. The median life expectancy is 31 months.[12]

Because metastatic breast cancer is incurable, the goals of treatment include extending overall survival, maintaining or improving quality of life, and controlling the disease (as measured by progression free survival, PFS). Although surgery or radiation therapy for palliation may be appropriate in select cases, the cornerstone of therapy consists of systemic therapeutics. Depending on the breast cancer subtype, systemic therapy may include hormone therapy, targeted therapy, or cytotoxic chemotherapy.

There are 4 subtypes of breast cancer as defined by gene expression profiling: luminal A, luminal B, HER2-enriched, and basal-type.[15] These subtypes are simplified through classical immunohistochemistry for estrogen-receptor (ER)/progesterone-receptor (PR), and HER2/neu (ERBB2 or simply HER2), leading to hormone-receptor positive breast cancer, HER2 amplified breast cancer (or HER2 positive), and triple-negative breast cancer. Each subtype is unique in its incidence, prognosis, and appropriate treatment algorithm.

Most breast cancers are hormonally driven. 65-70% of all breast cancers are ER positive (ER+) as detected by immunohistochemistry, making them potentially susceptible to endocrine therapies targeting this axis through systemic therapy.[13] Although most patients' disease will initially respond to endocrine therapy, eventually all patients will experience treatment failure. The selection and sequencing of hormone therapies are dependent on factors that include: patient's preference, comorbidities of the patient, performance status (PS) involvement of vital organs, pace of the disease, and previous history of exposure to treatments in the adjuvant (curative) setting. The most effective treatment tends to be the one first employed, making the selection of such first-line therapy critical to a patient's cancer journey. Second-line or later hormonal therapy without the addition of targeted therapy has led to response rates of <1%, and a PFS of < 3 months,[16] and although targeted agents have been shown to improve response rates and PFS, these improvements come with added toxicity and patient burden.

2.2 Accepted Clinical Practice

As advanced/metastatic breast cancer (mBC) is still considered to be incurable, the aim of therapy is to reverse (achieve remission) or to slow cancer progression with the hope of extending good quality life. This requires judgement in the selection a sequence of treatments that achieve a balance between potential efficacy and toxicity in individual patients.

2.2.1 Sequencing of available hormonal agents

The HR+/HER2 negative phenotype can be associated with indolent or slowly progressive disease, particularly in the early stages, and some form of hormonal therapy is usually recommended as initial therapy for patients with metastases. An exception is the presence of rapidly progressive visceral disease (eg. multiple liver metastases, pulmonary lymphangitis) where initial chemotherapy may be a better choice because of its more rapid effect.

Choices for hormone therapy include an antiestrogen (tamoxifen), aromatase inhibitors (AI) – non-steroidal (anastrozole, letrozole) or steroidal (exemestane), a selective ER down-regulator (fulvestrant) and, for premenopausal women, strategies to render them post-menopausal (ovarian ablation or suppression with LHRH agonists). In general, combinations of hormonal agents have not shown improved efficacy, although there are some conflicting data on fulvestrant combined with anastrozole.[17] More recently, improved efficacy (and increased toxicity) has been reported for combinations of targeted agents with AIs, specifically everolimus with exemestane [16,18] and palbociclib with letrozole.[19]

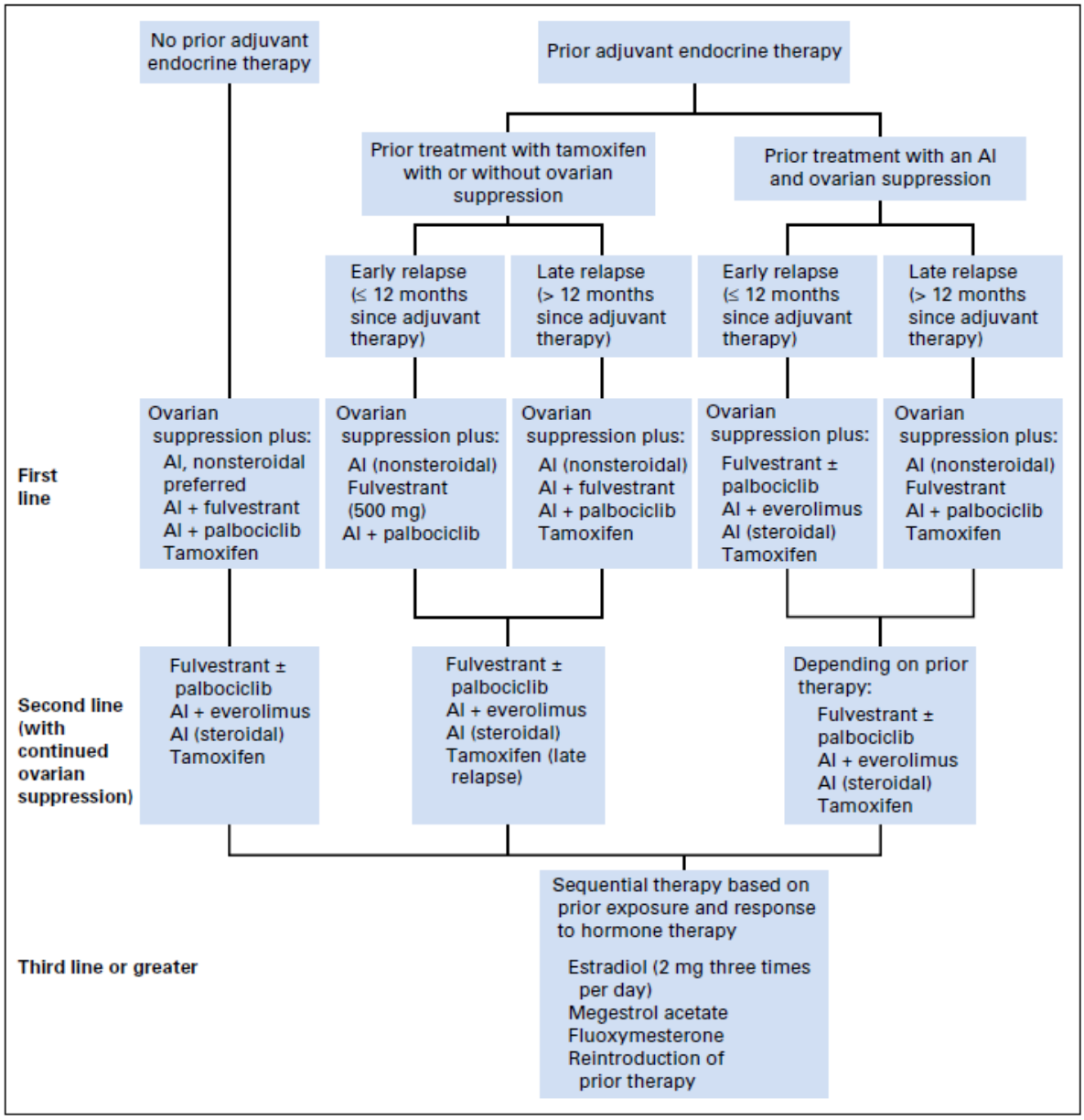
The optimum sequencing of the various hormonal therapies in HR+/HER2 negative mBC is complex, and has been the subject of several international guidelines – see algorithm from ASCO guideline.[12,17] Current Canadian practice is broadly consistent with recommendations in these guidelines but may be influenced by provincial funding restrictions.

Most postmenopausal patients with ER+/HER2 negative early breast cancer who subsequently relapse with metastatic disease are likely to have received adjuvant hormonal therapy with an AI or tamoxifen (or possibly both in the "switch" strategy, comprising 2 years of tamoxifen and 3 years of an AI, explored in several clinical trials). A minority will be hormone therapy-naïve because of contraindications, poor early tolerance, or presentation with low risk disease not requiring adjuvant hormone therapy. With the exception of those relapsing during or <12 months after the completion of adjuvant AI therapy, these women would be potential candidates for an AI (usually non-steroidal) as first-line therapy for mBC. In those with good PS who are willing to accept greater toxicity, a targeted agent such as palbociclib may be added. For patients presenting de-novo with mBC, the treatment recommendations are similar to those who are hormone therapy-naive.

After a variable duration of first-line hormone therapy, resistance develops and there is tumor progression. Options for second-line therapy will depend on prior exposure and response to first-line treatment. After relapse on a non-steroidal AI, treatment with a steroidal AI (exemestane) or tamoxifen can be considered. If exemestane is indicated, the targeted agent everolimus may be added, accepting that this regimen has greater toxicity that AI alone.

Women who remain premenopausal at the time of presentation with mBC usually are treated with tamoxifen. However, as AIs have been shown to have superior outcomes to tamoxifen in postmenopausal women in adjuvant and metastatic settings, some premenopausal women with mBC are now being considered for ovarian ablation or suppression, and then treated similarly to postmenopausal women. The added benefits are small, and this approach is associated with more toxicity and inconvenience (surgery or monthly injections), so many premenopausal women will opt for tamoxifen alone.

Treatment algorithm for HR+/HER2 negative locally advanced or metastatic breast cancer.[17]



Hormone therapy for premenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered at 500 mg every 2 weeks for three cycles, then monthly as an intramuscular injection. Withdrawal of tamoxifen or progestins was reported to result in short-term disease responses in older literature. Steroidal indicates exemestane; nonsteroidal indicates Anastrozole or letrozole. AI, aromatase inhibitor.

In the Canadian setting, availability of palbociclib, fulvestrant and everolimus in some settings are limited by Provincial reimbursement funding restrictions.

2.2.2 Non-steroidal aromatase inhibitor with palbociclib

Growth of HR+ breast cancer is dependent on cyclin-dependent kinase 4 and 6 (CDK4, CDK6) which promote progression from the G1 to S phase of the cell cycle. Palbociclib is an orally available highly selective inhibitor of CDK4 and CDK6, has high activity in HR+ cancer cell lines and is synergistic in combination with endocrine therapies.[20] In a small (165 patients) randomized trial, PALOMA-1,[21] there was a significant increase in PFS from 10.2 months with letrozole alone to 20.2 months for the combination of palbociclib plus letrozole (HR 0.49, p=0.0004). These results were confirmed in a larger (666 patients) double-blind placebo-controlled trial, PALOMA-2, with results first presented at the American Society of Clinical Oncology meeting in June 2016. Investigator–assessed median PFS was 24.8 months for the combination, compared with 14.5 months for letrozole alone (HR 0.58, p<0.000001). There were similar benefits in objective response and clinical benefit response rates. Toxicities were greater in the combination arm, especially grade ¾ neutropenia (54% versus 2%) but none were life-threatening. On the basis of these results, the final recommendation of pERC for pCODR (21 November 2016) was that palbociclib should be reimbursed conditional on the cost-effectiveness being improved to an acceptable level. This recommendation was for palbociclib combined with letrozole for postmenopausal women with HR+/HER2 negative mBC who had not received prior treatment for metastatic disease. A full manuscript describing the PALOMA-2 results was published 17 November 2016.[19] As of October 2018, most Canadian provinces had funded palbociclib with letrozole, generally restricting eligibility to postmenopausal women with ER+/HER2 negative advanced breast cancer who had received no prior systemic therapy.

2.2.3 Fulvestrant

Fulvestrant, a 17 beta-estradiol analog, is a selective ER agonist that suppresses estrogen signalling by binding to ER and inducing a conformational change. Dimerization is subsequently blocked, triggering accelerated degradation and down-regulation of the ER protein.[22] Early phase III trials of fulvestrant 250 mg LM monthly did not show superiority compared with anastrozole or tamoxifen.

Pharmacokinetic modelling suggested that the efficacy of fulvestrant could be improved with a higher dose, and a subsequent phase III trial, CONFIRM, compared fulvestrant 500 mg IM monthly (with a loading dose component) to 250 mg IM monthly, and showed improvement in PFS and OS[23] for the 500 mg dose regimen, which has now become the standard. In a randomized phase II study, FIRST, fulvestrant was compared with anastrozole in 205 patients, and showed improved clinical benefit response and PFS for fulvestrant when results were first reported, and an OS (HR 0.70, p=0.04) difference with longer follow up.[22] In a subsequent double-blind phase III trial (462 patients), FALCON, there was superior PFS for fulvestrant (HR 0.797, p=0.0486) compared with anastrozole.[24] On the basis of these results, the final recommendation of pERC for pCODR (1 February 2018) was that fulvestrant should be reimbursed conditional on its cost-effectiveness being improved to an acceptable level. This recommendation was for fulvestrant monotherapy in the treatment of postmenopausal women with non-visceral advanced or metastatic HR+/HER2 negative breast cancer who had not previously been treated with endocrine therapy (in adjuvant or metastatic settings). As of September 2018, the funding status for all provinces (excluding Quebec) is listed as “under negotiation with manufacturer”, so fulvestrant is not yet available across Canada except on a patient-pay or compassionate-funding basis.

2.2.4 Steroidal aromatase inhibitor (exemestane) with everolimus

One of the mechanisms of resistance to endocrine therapy is aberrant signalling through the phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) signalling pathway. Everolimus is a sirolimus derivative that inhibits mTOR through allosteric binding to mTORC1.[17] In a randomized phase II trial comparing neoadjuvant everolimus plus letrozole with letrozole alone in patients with newly diagnosed ER+ breast cancer, the response rate (by clinical palpation) for the combination was higher (68.1% vs 59.1%, p=0.062), and there was down-regulation of relevant biomarkers in the everolimus arm.[25]

In a subsequent randomized phase III trial, BOLERO-2, everolimus/exemestane was compared with everolimus/placebo in 724 women with ER+ mBC who had recurrence or progression while receiving a non-steroidal AI in the adjuvant setting and/or to treat metastatic disease. Median PFS was 10.6 versus 4.1 months (HR 0.36, p<0.001) in favor of the everolimus arm.[18] The most common grade ¾ adverse events in the everolimus arm were stomatitis (8%), anemia (6%), fatigue (4%) and dyspnea (4%). However, in a later publication,[16] median OS for everolimus/exemestane was not statistically superior, 31.0 versus 26.6 months (HR 0.89, p=0.14), although a 4.1 month prolongation of PFS persisted (p<0.0001).

Based on the PFS results, the final recommendation of pERC for pCODR (25 March 2013) was that everolimus in combination with exemestane should be funded conditional on the cost-effectiveness of everolimus being improved to an acceptable level. This recommendation was for treatment of HR+/HER2 negative mBC in women with ECOG PS </=2, after recurrence or progression following a non-steroidal AI, if the treating oncologist would consider using exemestane. By the end of 2014, most Canadian provinces had funded everolimus plus exemestane for the second-line treatment of postmenopausal women with ER+/HER2 negative mBC, although generally not after first-line treatment with palbociclib.

2.3 Evidence-Based Considerations for a Funding Population

The requested indication for funding is for the combination of palbociclib with fulvestrant for the treatment of women with HR+/HER2 negative locally advanced or metastatic breast cancer whose disease has progressed after prior endocrine therapy (ie. second-line treatment for mBC). Pre- or perimenopausal women must also undergo ovarian ablation or suppression with an LHRH agonist. In the PALOMA-3 study, postmenopausal women were required to have progression on prior AI therapy for metastatic disease, or within 12 months of completing adjuvant AI therapy, with the same criteria applying to previous tamoxifen therapy for premenopausal women. Prior neoadjuvant/adjuvant chemotherapy was permitted, and women could have received one line of chemotherapy for mBC. All trial participants had ECOG PS 0-1.

Because of the multiple hormone +/- targeted therapy options available for mBC, determined by complex algorithms, the size of the patient population eligible for palbociclib + fulvestrant is difficult to estimate. However, given the slowly progressive nature of endocrine-sensitive disease it is likely that most women will survive to receive second-line hormone therapy for mBC. With funding available for palbociclib plus letrozole as first-line therapy for the same population, as many as 50-60 % of patients presenting with mBC will not be eligible for treatment with palbociclib plus fulvestrant second-line. Thus, in postmenopausal women, palbociclib plus fulvestrant is most likely to be given to a limited number of patients who were not eligible for a variety of reasons for first-line palbociclib plus letrozole (eg. received

AI treatment for mBC before palbociclib was available, chose not to receive it, or had a contraindication to palbociclib which is no longer operative). The main competing alternative treatments would be exemestane, with or without everolimus, tamoxifen or single agent fulvestrant.

Patients previously treated with tamoxifen who remain premenopausal, to date have had limited further hormonal options, and would be good candidates for this therapy, which in PALOMA-3 was shown to be as active in premenopausal women undergoing ovarian ablation or suppression, as in the main postmenopausal cohort.[26] This contrasts with the patient population evaluated in PALOMA-2, receiving palbociclib plus letrozole, which was entirely postmenopausal.

2.4 Other Patient Populations in Whom the Drug May Be Used

In patients with good PS who have never received a CDK 4,6 inhibitor, clinicians may wish to use palbociclib with fulvestrant as a third-line hormonal manipulation. For example, in patients treated first-line with a non-steroidal AI, and second-line with everolimus plus exemestane, this may be an attractive option. Another possibility is the use of palbociclib plus fulvestrant after more than one line of chemotherapy for mBC. In the PALOMA-3 trial, investigators stated that palbociclib plus fulvestrant was well-tolerated with the primary toxicity being asymptomatic neutropenia that was effectively managed by dose modification without loss of efficacy,[27] and clinicians also wish to consider this treatment for women with lower PS =/< 2).

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Patient input regarding palbociclib (Ibrance) use in combination with fulvestrant for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer was provided by two patient advocacy groups: Rethink Breast Cancer (RBC) and the Canadian Breast Cancer Network (CBCN). Their methods and input are summarized below.

RBC gathered data by way of online surveys and one-to-one interviews with patients. Online surveys were conducted between August 8 and October 5, 2018. Potential respondents were identified through messages to ReThink Breast Cancer's mailing list as well as the Young Women's Network and partner organizations. Messages were also posted on Facebook and Twitter as well as the Breastcancer.org, Cancer Connection and Cancer
Survivors Network online discussion forums. A total of 26 women completed the survey. Of these, 10 were from Canada (representing AB, BC, NB, NL, ON, QC and YK), fourteen were from the US, one from Germany and one from Lebanon. Twenty-four of the respondents were diagnosed with HR-positive, HER2-negative metastatic breast cancer and 18 respondents have experience with palbociclib in combination with fulvestrant. Online participants were solicited for follow-up interviews and four women accepted to participate.

CBCN obtained information from four sources:

1) The CBCN 2017 Survey of Metastatic Breast Cancer Patients. This online survey collected comprehensive data from 180 Canadians living with metastatic breast cancer. It is unknown whether or not patients who participated in this survey had experience with the treatment under review. Patients were contacted through CBCN's patient network, website and social media. Results were published in October 2018 in the report entitled "Breast cancer: The Lived Experience" (available at https://cbcn.ca/en/the-lived-experience).
2) The CBCN 2012 Metastatic Breast Cancer Patient and Caregiver Survey. This online survey, conducted in collaboration with ReThink Breast Cancer, was distributed to patients living with metastatic breast cancer and their caregivers. No patients surveyed had experience with the treatment under review. Patients were contacted through the membership databases of CBCN and other patient organizations. Seventy-one patients and 16 caregivers participated in the survey.
3) Key Informant Interviews. Phone interviews were conducted by CBCN in August and September 2018 with 8 Canadian patients living with HR-positive HER2-negative metastatic or advanced breast cancer, who had disease progression after endocrine therapy and had direct experience with the treatment under review.
4) Printed sources. CBCN conducted a review of current studies and grey literature to identify issues and experiences that are commonly shared among many women living with breast cancer.

From a patient perspective, metastatic breast cancer is severely debilitating and associated with pain, fatigue, and impaired ability to perform regular life activities such as working, driving and spending time with family and friends. Diagnosis of metastatic breast cancer was generally detrimental to the mental health of patients and to their finances.
According to patients, current therapeutic options cause a number of side effects, fatigue being the most difficult to tolerate. Financial challenges due to treatment were identified as a major issue. Patients with a diagnosis of metastatic breast cancer understand the limitations and toxicities of current treatment options and seek to obtain the best quality of life that can be achieved in the time that is available.

Patients who had experience with the drug combination under review had a favourable outlook on the therapy. Overall, patients felt that the treatment led to a modest improvement in quality of life and a substantial improvement in disease control. Toxicity was noticeably milder and more tolerable than with other options.

Patient goals, values and expectations were centred on better progression-free survival and a sustained quality of life. Side effects were not a major consideration to patients and some measure of toxicity was deemed acceptable so long as disease control was achieved.

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

Of all 26 participants responding to the RBC survey, 4 were receiving first-line treatment, 2 were receiving second-line treatment, 2 were receiving third-line treatment or higher, 6 were receiving treatment after recurrence, 1 was watching and waiting, 2 have had no evidence of disease for less than six months, 2 have had no evidence of disease for between six months and two years, and 7 indicated they were in a different phase of treatment. RBC provided an analysis of its survey results, reproduced in Table 1.

Table 1: RBC Survey Results

Impact of breast cancer symptoms on the lives of patients	1 - no impact	2	3	4	5 - significant impact	Average
Ability to work	32% 8	4% 1	8% 2	20% 5	36% 9	3.24 25
Ability to sleep	16% 4	20% 5	12% 3	24% 6	28% 7	3.28 25
Ability to drive	50% 12	21% 5	17% 4	0% 0	13% 3	2.04 25
Ability to travel	28% 7	32% 8	16% 4	4% 1	20% 5	2.36 25
Ability to exercise	20% 5	12% 3	32% 8	16% 4	20% 5	3.04 25
Ability to perform household chores	20% 5	28% 7	36% 9	4% 1	12% 3	2.60 25
Ability to care for children	36% 8	14% 3	23% 5	9% 2	18% 4	2.59 22
Ability to fulfill family obligations	28% 7	24% 6	16% 4	16% 4	16% 4	2.68 25
Ability to spend time with family and friends	36% 9	12% 3	28% 7	12% 3	12% 3	2.52 25

CBCN's 2012 Metastatic Breast Cancer and Caregiver Survey paints a similar picture of the physical impact of the disease on patient experience. For fatigue, 54% respondents reported a significant or debilitating impact, and 40% reported some or moderate impact. Thirty-nine percent of patients 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.

Complementary to the latter, CBCN's 2017 Patient Survey provided the experience regarding the social impact of metastatic breast cancer. CBCN noted that the disease affects all aspects of a patient's life, restricting employment and career prospects, the ability to care for children and dependents, and the ability to socially and meaningfully participate in the community. At the time of diagnosis, 47% of respondents were employed full-time, while only 12% remained employed full time at the time of the survey. As a result of the diagnosis, 74% of respondents experienced an impact on their mental health; 42% reported some negative impact on their finances and 40% reported a large impact. The 2012 CBCN survey had quality of life results largely in line with the RBC survey, as seen in Table 2.

Table 2: CBCN 2012 Survey Results Regarding Quality of Life

	Some/moderate restrictions	Significant restrictions
Ability to exercise	49%	38%
Ability to pursue hobbies an personal interests	42%	42%
Ability to participate in social events and activities	41%	41%
Ability to spend time with loved ones	22%	52%

Patients responding to CBCN survey mentioned other experiences 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, and martial stress or loss of fidelity and affection from partner. CBCN provided a quote from a breast cancer patient responding to the 2017 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 has bombarded my family and me with… the most difficult aspect is planning for my mortality and trying to keep my chin up and not burden my family."

3.1.2 Patients' Experiences with Current Therapy for Metastatic Breast Cancer

RBC provided detailed information about the treatments that the 26 survey respondents underwent since diagnosis. Excluding palbociclib and fulvestrant, letrozole and tamoxifen were the most common forms of treatment (see Table 3 for more details). CBCN did not describe treatments experienced by their survey respondents.

Table 3: Treatments experienced by RBC respondents

Treatments Received	n	Treatments Received	n
Letrozole (Femara)	16	Paclitaxel (Taxol)	2
Tamoxifen (Nolvadex)	12	Ribociclib (Kisqali)	1
Goserelin (Zoladex)	7	Denosumab (Xgeva)	1
Anastrazole (Arimidex)	3	Docetaxel (Taxotere)	1
Exemestane (Aromasin)	3	Everolimus (Afinitor)	1
Capecitabine (Xeloda)	3	Zoledronate (Zometa)	1
Pamidronate (Aredia)	3	Cyclophosphamide (Cytoxan)	1

Results from the RBC survey also provided information on the side effects caused by these treatments. Fatigue was the most commonly reported side effect (88%, n=25), followed by insomnia (48%), nausea and constipation (40% for each). Fatigue was also the most difficult side effect to tolerate according to 10 patients; no other symptom was listed more than once.

Financial challenges were identified as an important issue for patients (n=25) responding to the RBC survey, with travel costs (48%), lost income due to work absence (44%), drug costs (28%) and parking costs (24%) being the most commonly mentioned issues. However, it should be noted that only one of one of the respondents who identified drug costs as a challenge was from Canada. Forty percent of respondents reported requiring financial assistance due to costs associated with cancer and its treatment.

The latter issue was shared by patients responding to the CBCN surveys or reported in the literature that was presented by CBCN. A 2010 study conducted by CBCN indicates that 80% of Canadian breast cancer patients report a financial impact due to their illness, and that 44% have used their saving and 27% have taken on debt to cover costs. According to the 2017 survey, the financial burden of treating and managing breast cancer directly impacted whether or not patient adhered to cancer treatments or supportive medications. Thirty-nine percent of survey respondents indicated having been prescribed medication that were not covered by the public health care system and 8% didn't take their medication due to cost. For support medication, the proportions were 85% and 7%, respectively.

Other barriers mentioned in the CBCN survey include: not qualifying for insurance at work, inability to change employers due to loss of insurance, and the prohibitive cost of new treatment options. As one survey respondent puts:

"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 raised the issue of availability of health care services and child care in the community while the patient is on treatment. Among patients with children or other dependents, 53% indicated that there is minimal or no access to appropriate care for their loved ones when they are experiencing debilitating symptoms related to their cancer, and 40% identified barriers to accessing quality care during cancer treatment.

CBCN suggested that in view of responses to open-ended survey questions (both 2012 and 2017), all women with metastatic breast cancer should have the option to access new treatments that have proven efficacy. It was stressed that most patients are well aware of adverse effects and want to make a personal choice. The importance of choice and trade-offs is illustrated by the following quote from a patient responding to the 2012 survey:

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

Finally, CBCN remarked that current treatment options for hormone receptor positive metastatic breast cancer are only effective at prolonging progression-free disease, and most cases of advanced disease will progress and symptoms will worsen. Patients with a diagnosis of metastatic breast cancer understand the limitations of current treatment options, and seek to live their remaining months and years with the best quality of life that they can achieve.

3.1.3 Impact of Metastatic Breast Cancer and Current Therapy on Caregivers

No information was available on caregiver perspective.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Experiences with Palbociclib plus Fulvestrant

Eighteen participants of the RBC survey had been treated with palbociclib in combination with fulvestrant. Of these, 17 indicated having been diagnosed with HR+, HER2- metastatic breast cancer (one declined to answer). Twelve respondents received other treatments priori to palbociclib and 4 experienced disease progression on other endocrine therapy. Patients rated the change to their quality of life on palbociclib compared to other therapies they had received. A detailed breakdown of answers is presented in Table 4 below. Overall, respondents felt that the palbociclib-based treatment led to a modest improvement in quality of life and a substantial improvement in disease control. The patients expressed a preference for prioritizing disease control and the vast majority believed that palbociclib had such an effect.

Table 4: Patient experienced regard palbociclib/fulvestrant treatment

Change while on palbociclib	1 – much worse	2	3	4	5 – much better	Average
Metastatic cancer symptoms	0 % 0	14% 2	29% 4	14 % 2	43% 6	3.86 14
Drug side effects	6% 1	25% 4	31% 5	6% 1	31% 5	3.31 16
Maintaining quality of life	0% 0	6% 1	38% 6	19% 3	38% 6	3.88 16
Controlling disease	0% 0	0% 0	13% 2	13% 2	73% 11	4.60 15

One breast cancer patient taking palbociclib as a third line treatment made the following comment:

"I feel healthier than I have in years I work out with personal trainer 2x/wk, swim. walk my dogs, travel, and generally enjoy life."

CBCN collected the perspective of 8 Canadian patients with various levels of experience with palbociclib combined with fulvestrant. All patients received some form of treatment prior to being put on the new drug combination. Length of treatment history ranged from 2 months to over 2 years. Six of the patients expressed their overall satisfaction with the treatment under review in terms of disease management and quality of life. Examples of patient comments about therapy include:

"I've been on it for about a year. I do have limited tumour growth but it seems to be mostly under control"

"[Treatment] has been ineffective, because I've had progression"

"At my last CT scan, everything was stable. My oncologist was very happy with the result. I have had tumours in my liver that have shrunk."

Patients consulted by CBCN expressed their preference for this treatment over the alternative of chemotherapy. They provided comments such as:

"I could have had chemotherapy. This is much preferable. I don't want to lose my hair. I don't want to get sick. This is not invasive at all."

Treatment with palbociclib and fulvestrant led to successful disease control in seven of the eight CBCN patients. These patients reported positive impact on their quality of life.

RBC recorded patient experiences (n=17) regarding side effects associated with palbociclib. More than half gave their side effects a score of less than 5 on a scale of 1 (completely tolerable) to 10 (completely intolerable), with an average score of 4.47. Fatigue (82%) and neutropenia (65%) were the most commonly cited side effects associated with palbociclib. A patient on first line palbociclib explained that *"the side effects that come with this, to me, are just so easy compared to … classic chemo, radiation and surgery, so, at this point, I just think this is a lot easier."*

Similarly, CBCN compiled patient feedback on side effects caused by palbociclib/fulvestrant. Seven of the eight patients reported side effects which included fatigue, hair thinning, diarrhea, sore mouth and neutropenia. Some patients were taking additional medication to manage the side effects, but most were able to manage them with rest, laxatives and a controlled diet. All patients interviewed indicated that the side effects they experienced were acceptable. The following are select patient quotes about the side effects from the drug combination:

"The side effects are not horrendous. I'm much more tired than I used to be, and I don't know what to attribute that to."

"I have higher levels of fatigue and some stomach issues. I also notice that I have higher levels of anxiety. That's really become [an] issue in the last couple of years. And it's hard to know with anxiety whether that's drug-related or situation-related."

According to CBCN, no issue regarding drug administration was raised by patients. A requirement regarding white blood cell counts was a minor challenge to one patient as it limited her ability to travel. Several patients noted that they would not be able to afford the drug would it not be covered by a drug plan. One patient said:

"I'm just grateful to have received funding. I have two health plans. But it would have been a huge sacrifice for me to actually have to try to pay. It probably would have involved selling a house […]"

3.2.2 Patient Expectations for Palbociclib plus Fulvestrant

RBC provided a detailed assessment of outcomes that are valued by patients with metastatic breast cancer. Results are presented in Table 5. Overall, respondents prized long-term health outcomes with 25 out of 26 patients giving the highest score for controlling disease and 24 out of 26 for preventing recurrence and maintaining quality of life. One patient in remission declared:

"My goal is to live another 30+ years and given the new treatments, I have a chance."

Table 5: Outcomes valued by patients surveyed by RBC

Importance of outcome	1 - not important	2	3	4	5 – very important	Average
Controlling disease	0 % 0	0% 0	0% 0	4% 1	96% 25	4.96% 26
Reducing symptoms	0 % 0	8% 2	15% 4	19% 5	58% 15	4.27 26
Maintaining quality of life	0% 0	0% 0	8% 2	0% 0	92% 24	4.85 26
Managing side effects	0% 0	4% 1	12% 3	15% 4	69% 18	4.50 26
Preventing recurrence	8% 2	0% 0	0% 0	0% 0	92% 24	4.69 26

CBCN also indicated that progression-free survival is a chief concern for patients and is expected to be extended with palbociclib/fulvestrant treatment. The goal for these patients is to obtain a better quality of life compared with chemotherapy or other more toxic therapies. Patients interviewed by CBCN who were receiving palbociclib plus fulvestrant stressed the importance of having diverse treatment options available to them and other patients particularly so that they could avoid having to turn to chemotherapy as a treatment option. Patients embrace opportunities to try new treatments, even if benefits may be as little as a six month of progression-free survival. They hope for a sustained quality of life while on treatment, for example by *"[having] the energy to attend their children's/grandchildren's activities and to spend time with family and friends."*

RBC survey respondents were asked about their expectations regarding side effects from any new drugs that could control disease progression or prevent recurrence. All but one patient gave a score indicating that they would tolerate side effects to some extent in these circumstances. Some patients added:

"I will tolerate as many side effects as I could in order to keep disease away."

"I can deal with these [side effects] for however long I need to deal with these because I'm living."

The CBCN survey also captured information on side effects and the willingness of patients to tolerate them. 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 six months. They generally answered that this assessment can only be determined by an individual patient, in this circumstance. Close to 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. In regards to pain, 70% of patients said that 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.

3.3 Companion Diagnostic Test

Patient groups did not provide input on this aspect.

3.4 Additional Information

All 17 patients from the RBC survey who had experience with palbociclib indicated they would recommend the drug to other patients with metastatic breast cancer. Some of these patients provided additional comments summarizing their experience. For example, a patient on second-line treatment declared:

"This is the easiest drug combo that I have done. Symptoms are minimal and managed with OTC meds for constipation and insomnia".

Another patient on treatment after disease recurrence wrote:

"My experience has been wonderful as far as any cancer treatment. Side effects are tolerable, more so than other treatments and allows for increased quality of life."

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. 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:

- Fulvestrant is not publically funded in any provinces for metastatic breast cancer
- Monthly monitoring and bloodwork for neutropenia with palbociclib as well as treatment visits for fulvestrant

Economic factors:

- Large number of patients eligible for treatment
- Potential for drug wastage due to dose adjustments

Please see below for more details.

4.1 Currently Funded Treatments

Various treatments are available for patients with metastatic breast cancer previously treated with endocrine therapy. These include exemestane plus everolimus, tamoxifen, and chemotherapy. PAG noted that the comparator in the PALOMA-3 trial was fulvestrant and fulvestrant is not publically funded in any provinces for metastatic breast cancer. PAG is seeking information on data comparing palbociclib plus fulvestrant to currently available treatments. Exemestane plus everolimus is not funded after palbociclib plus letrozole in the first-line setting.

4.2 Eligible Patient Population

PAG noted that the following groups of patients were not included in the PALOMA-3 trial and are seeking guidance on the appropriateness of palbociclib plus fulvestrant for,

- Male patients with breast cancer
- Those who had extensive symptomatic visceral metastasis
- Those who had uncontrolled CNS metastases
- Those who had an Eastern Cooperative Oncology Group performance status of 2
- Those who are HER2 double equivocal (both IHC and ISH/FISH are equivocal)

In the trial, disease relapse or progression had to occur after previous endocrine therapy while on or within 1 month after treatment in the advanced setting, or while on or within 12 months of completion of adjuvant therapy. One previous line of chemotherapy in advanced disease was allowed. PAG is seeking clarity whether patients who had received previous systemic chemotherapy and endocrine therapy would be eligible as the first-line trials of palbociclib excluded patients who received previous systemic chemotherapy. PAG is also seeking confirmation that eligibility with respect to timing of disease relapse or progression on endocrine therapy in the adjuvant or advanced setting would align with that in the PALOMA-3 trial.

PAG noted patients were excluded if they had previously received any CDK inhibitor. PAG

is seeking confirmation that patients treated with a first-line CDK inhibitor (i.e., palbociclib, ribociclib) plus an aromatase inhibitor would not be eligible for palbociclib plus fulvestrant. PAG noted that the current reimbursement criteria for first-line treatment with palbociclib excluded several populations noted above.

If recommended for reimbursement, PAG noted the following groups of patients would need to be addressed on a time-limited basis:

- Patients who recently started on single agent fulvestrant
- Patients who recently started chemotherapy for relapsed disease
- Patients already treated or currently treated with everolimus plus exemestane
- Patients who have progressed on or are currently on second-line endocrine therapy

If recommended for reimbursement, PAG is seeking guidance on the appropriateness, for patients who received palbociclib plus an aromatase inhibitor in the first-line setting and who start progressing, to continue on with palbociclib but switch the aromatase inhibitor for fulvestrant.

4.3 Implementation Factors

PAG noted that this is a large patient population.

PAG noted that additional health care resources may be required to monitor and treat toxicities and monitor drug-drug interactions. Due to the high incidence of neutropenia with the addition of palbociclib, patients will need to be seen monthly for monitoring and bloodwork. PAG also noted for patients who are pre or peri-menopausal and require a GnRH agonist to chemically induce menopause, this would increase clinic visits for administration and overall costs to the regimen.

The dose of palbociclib is well-known, this is an enabler to implementation. The availability of three different strengths facilitates dose adjustments as the capsule strengths correlate with the dose adjustments. There are some concerns with the potential for drug wastage for patients who may be dispensed one strength but dose adjustments occur prior to finishing the amount dispensed. As palbociclib is administered orally, chemotherapy units and chair time would not be required. As an oral drug, palbociclib 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.

Fulvestrant monotherapy was previously reviewed for locally advanced or metastatic HER2- breast cancer with non-visceral disease, who have not been previously treated with endocrine therapy. At the time of this PAG input, fulvestrant is not yet 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 requires incremental resources over patients who receive oral endocrine therapy.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate sequencing of all available treatments for ER+, HER2- advanced breast cancer. For patients who receive palbociclib plus fulvestrant and then develop metastatic disease,

- What treatments can they receive following palbociclib plus fulvestrant?
- How should everolimus plus exemestane be sequenced? As previously mentioned, this combination is not funded after palbociclib plus letrozole in the first-line setting.

PAG is also seeking guidance on the interchangeability of CDK inhibitor (i.e., palbociclib, ribociclib) in this setting. PAG recognizes that there may not be data on the use of palbociclib plus fulvestrant in the first-line setting ahead of endocrine therapy, but indicated there may be pressure from oncologists and patients to use palbociclib plus fulvestrant as first-line.

4.5 Companion Diagnostic Testing

None.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Four inputs from clinicians were received by pCODR: a submission from BC Cancer providing the perspective of a single oncologist, a joint submission from Cancer Care Ontario capturing the perspective of four clinicians (three oncologists and one oncology pharmacist), a joint submission from Alberta Health Services representing three oncologists, and one individual input from an oncologist at the Ottawa Hospital Cancer Centre, for a total of nine clinicians providing input.

The clinicians who provided input noted that there are limited treatment options for patients with metastatic hormone receptor (HR) positive, HER2-negative breast cancer who have progressed on previous endocrine therapy. These patients represent a large population and continued treatment with alternate endocrine and other non-chemotherapeutic approaches is generally preferred by clinicians. Clinicians consider palbociclib plus fulvestrant to be a safe and effective line of therapy for patients who have developed resistance to endocrine therapy including aromatase inhibitors. This combination would naturally replace second line aromatase inhibitors. Clinicians value the potential choice of using palbociclib in either the first or second line setting.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for Metastatic Breast Cancer

According to clinicians providing input, few treatments are available for patients with metastatic HR-positive, HER2-negative breast cancer who have progressed on previous endocrine therapy. These include exemestane plus everolimus, tamoxifen, and chemotherapy.

For most patients, a second endocrine agent is given, such as an alternate aromatase inhibitor (letrozole, anastrozole, exemestane) as per international guidelines. Fulvestrant is a preferred backbone option, but it is not currently publically funded and only available to patients with private coverage or the means to pay. Chemotherapy would be used in the minority of patients with severe organ involvement or very rapidly, progressive, symptomatic disease.

Since fulvestrant is not publicly funded in any provinces for metastatic breast cancer (MBC) treatment options outside systemic chemotherapy, tamoxifen and exemestane plus everolimus are limited.

5.2 Eligible Patient Population

Clinicians providing input noted that they commonly come across patients with a disease matching the funding request and most patients with MBC will be offered a second line endocrine drug. The time on second line therapy will be 1-2 years, but the population will be relatively large. The latter would also include patients who recur during or within 12 months of adjuvant therapy.

Clinicians clarified that palbociclib and fulvestrant would be useful for patients who elected to undergo endocrine monotherapy in the first line setting (tamoxifen or an aromatase inhibitor) and progressed, whether or not they also underwent systemic chemotherapy. This would be in line with the trial criteria of the PALOMA-3 trial and aligns with clinical practice.

Clinicians affirmed that there is an unmet need in this population since not all patients with HR+/HER2- MBC currently meet eligibility for an aromatase inhibitor plus palbociclib. These include a) patients treated with single agent endocrine therapy upfront, b) patients who relapse on or within 12 months of finishing adjuvant endocrine therapy and need an alternative to exemestane plus everolimus, and c) patients exposed to a line of chemotherapy in the metastatic setting before or

after progression on single-agent endocrine therapy.

5.3 Relevance to Clinical Practice

All clinicians submitting input had experience with using palbociclib plus fulvestrant in this setting. Clinicians would use the treatment in those eligible as described above, particularly those with unmet need. Use of this treatment would help delay systemic chemotherapy in the metastatic setting.

Clinicians believe that palbociclib and fulvestrant constitute an advantageous treatment strategy to overcome primary endocrine resistance. Clinicians reasoned that since fulvestrant plus palbociclib is more effective than fulvestrant alone, the combination is also likely more effective than next line single-agent hormonal therapy and hence would be preferred. They also argued that genetic resistance to endocrine agents (especially aromatase inhibitors) would not extend to fulvestrant, making it the ideal next line agent. Palbociclib would further improve progression-free survival (PFS) in all subsets. According to clinicians, PFS improvement is clinically meaningful and substantially delays symptomatic deterioration and the need for chemotherapy. According to a clinician, there is no PFS data comparing palbociclib plus fulvestrant to with exemestane plus everolimus or chemotherapy, but the side effect profile of palbociclib plus fulvestrant appears more favourable than what one would normally see with the latter options. Exemestane plus everolimus is often poorly tolerated due to mucositis, nausea, diarrhea and rash, and may particularly affect patients with significant lung disease not related to cancer. One clinician input observed that the hazard ratio associated with palbociclib and fulvestrant is similar to that of first line palbociclib and letrozole, and the benefits are equally impressive.

Some clinicians indicated that clinicians should have the choice of when to use a CDK4/6 inhibitor either as first or second line depending on patient factors. Patients who decide to undergo first line endocrine monotherapy should not be excluded from accessing a CDK4/6 inhibitor as a later treatment line option upon progression. It may be better to give access to a CDK4/6 inhibitor upon progression on endocrine therapy rather than adding the CDK4/6 inhibitor to those who are doing well in the first line endocrine setting. The new drug combination would also allow treatment of premenopausal women, a group that is currently excluded from first line palbociclib funding.

A clinician reported their experience with women who have been on this combination (or first line palbociclib). Overall, toxicity was very tolerable in the long term and clinical response was favourable especially in view of poor prognosis beyond first line.

5.4 Sequencing and Priority of Treatments with Palbociclib plus Fulvestrant

The clinicians providing input believed that the therapy would be offered to women with MBC who have progressed after one or two prior lines of therapy. These patients would have relapsed on or within 12 months of adjuvant endocrine therapy or progressed on or within 1 month of endocrine therapy, including single agent endocrine therapy (tamoxifen or an aromatase inhibitor). Clinicians still see a role for palbociclib plus an aromatase inhibitor as first-line therapy in the majority of patients. Clinicians surmise that palbociclib plus fulvestrant would replace second line aromatase inhibitors.

According to some clinicians, having this new second-line option may indirectly prompt clinicians to more often consider single agent aromatase inhibitors alone in the first line setting as it would not deprive patients of the potential benefits of CDK4/6 inhibitors at some point in their treatment. While this class is deemed important in MBC therapy, the current funding model imposing first line CDK4/6 inhibitors is seen as costly due to the longer duration of treatment.

In light of pre-clinical data suggesting that exemestane plus everolimus are effective after exposure to CDK4/6 inhibitors, clinicians would consider this combination (if available) after palbociclib plus fulvestrant and would prefer to reserve chemotherapy after all endocrine therapies have been exhausted. Nevertheless, some patients with visceral crisis may be better candidates for chemotherapy after progression on the treatment under review.

5.5 Companion Diagnostic Testing

The clinicians did not consider this question to be applicable since no biomarker has been found helpful in selecting patients for this drug combination. ER/PR and HER2 testing is already standard practice.

5.6 Additional Information

None.

5.7 Implementation Question

5.7.1 In clinical practice, is there a preference to use palbociclib in combination with an aromatase inhibitor in the first-line setting or in combination with fulvestrant in the second-line setting?

According to clinicians, first line palbociclib would be preferred as the PFS benefit is greater. However, individual factors may call for a simplified regimen including aromatase inhibitor monotherapy. For instance, some patients who declined palbociclib and stayed on letrozole monotherapy were concerned about convenience and quality of life. Those same patients may later seek treatment with palbociclib should they progress on the aromatase inhibitor.

5.7.2 In clinical practice, what treatment options would be available to patients upon progression of palbociclib plus fulvestrant? Which sequence of treatments would be preferred?

Clinicians stated that most patients from Ontario would be treated with chemotherapy upon progression. The following non-chemotherapeutic options were mentioned: tamoxifen, additional aromatase inhibitors, megestrol acetate, exemestane, or access to drugs in clinical trials. Preference would be determined by prior endocrine sensitivity, extent of disease and patient preference.

5.7.3 For patients with HER2 double equivocal (equivocal by IHC and ISH/FISH), would you use palbociclib plus fulvestrant?

Clinicians responded in the affirmative as those patients would not qualify as HER2 positive according to the new ASCO/CAP guidelines. It was noted that these patients are not eligible for targeted therapy with trastuzumab, pertuzumab, or other HER2-directed agents.

5.7.4 In the PALOMA-3 trial, patients were excluded if they had extensive symptomatic visceral metastases. Based on your experience, would you treat patients with visceral disease with palbociclib plus fulvestrant?

Some clinicians responded that they would treat such patients conditional on reasonable safety threshold and a significant prior response to hormone therapy. Clinicians observed that some (breast) cancers are more hormone-sensitive that chemo-sensitive and that is not necessarily indicated by site of metastasis. Other clinicians would opt to exclude patients with extensive and symptomatic metastases from treatment, as per PALOMA3, but would

still treat patients with less extensive visceral disease. Clinicians preferred to use chemotherapy for patients with extensive, very symptomatic and potentially life-threatening visceral disease. It was noted that using chemotherapy first would prevent a patient from accessing targeted endocrine therapy treatment options in the future under the current (first line) palbociclib funding criteria.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of palbociclib in combination with fulvestrant (palbociclib + fulvestrant) in the treatment of women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) locally advanced breast cancer (ABC) or metastatic breast cancer (mBC) who progressed after prior endocrine therapy.

Note: Supplemental questions 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.

Supplemental question:

- Critical appraisal of a manufacturer-submitted network meta-analysis comparing palbociclib + fulvestrant with other available endocrine-based treatment options currently approved for the treatment of women with HR+/HER2- locally ABC or mBC after progression on endocrine therapy

6.2 Methods

6.2.1. Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 6.1. Outcomes considered most relevant to patients, based on input from patient advocacy groups, are indicated in bold.

Table 6.1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized controlled trials	Adult (≥18 years) postmenopausal and pre/peri-menopausal women with HR+/HER2- locally ABC or mBC who progressed after prior endocrine therapy (2nd+ line). Subgroups: – ECOG PS (0 vs 1 vs 2) – Menopausal Status (pre-/peri-menopausal vs. post-menopausal) – Non-measurable disease (bone vs. other) – Measurable disease (visceral, lung , liver, peritoneal, brain, or pleural) – Previous lines of endocrine treatment (1 vs. 2, vs. ≥3) – Disease-free interval (≥24 months vs 12-24 months vs. <12 months)	palbociclib + fulvestrant *PALOMA-3 trial doses:* *palbociclib (oral; 125 mg QD; 3 weeks on/1 week off)* + *fulvestrant (IM; 500 mg q4w)* *All pre- or peri-menopausal women were also treated with an LHRH agonist*	fulvestrant ± placebo (PALOMA-3 trial comparator) Other endocrine therapy options, including: – Aromatase inhibitors (letrozole, anastrozole, and exemestane.33 letrozole and anastrozole) – Selective estrogen receptor modulators (e.g., tamoxifen) Chemotherapy, including: – Anthracyclines (doxorubicin, pegylated liposomal doxorubicin, or epirubicin)	**Efficacy** – **Progression-free survival** – Overall survival – Objective response rate – Duration of response – Clinical benefit** **Patient-reported outcomes/HRQoL** **Safety** – AEs – SAEs – WDAEs

Table 6.1: Selection Criteria				
Clinical Trial Design	**Patient Population**	**Intervention**	**Appropriate Comparators***	**Outcomes**
	– Previous endocrine therapy (aromatase inhibitors vs. tamoxifen vs. aromatase inhibitors + tamoxifen – Previous chemotherapy (neoadjuvant or adjuvant therapy only vs. treatment of metastatic disease [± adjuvant / neoadjuvant]) – Previous sensitivity to endocrine therapy (Yes vs No)		– Taxanes (paclitaxel, docetaxel, or albumin-bound paclitaxel) – Antimetabolites (capecitabine or gemcitabine) – Microtubule inhibitors (vinorelbine or eribulin)	

ABC = locally advanced breast cancer; **AE** = adverse event; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status Scale; **HER2** = human epidermal growth factor receptor 2; **HR** = hormone receptor; **HRQoL** = health-related quality of life; **IM** = intramuscular injection; **LHRH** = Luteinizing hormone-releasing hormone; **mBC** = metastatic breast cancer; **mg** = milligram; **q4w** = every 4 weeks; **QD** = per day; **SAE** = serious adverse events; **vs.** = versus; **WDAE** = withdrawals due to adverse events.

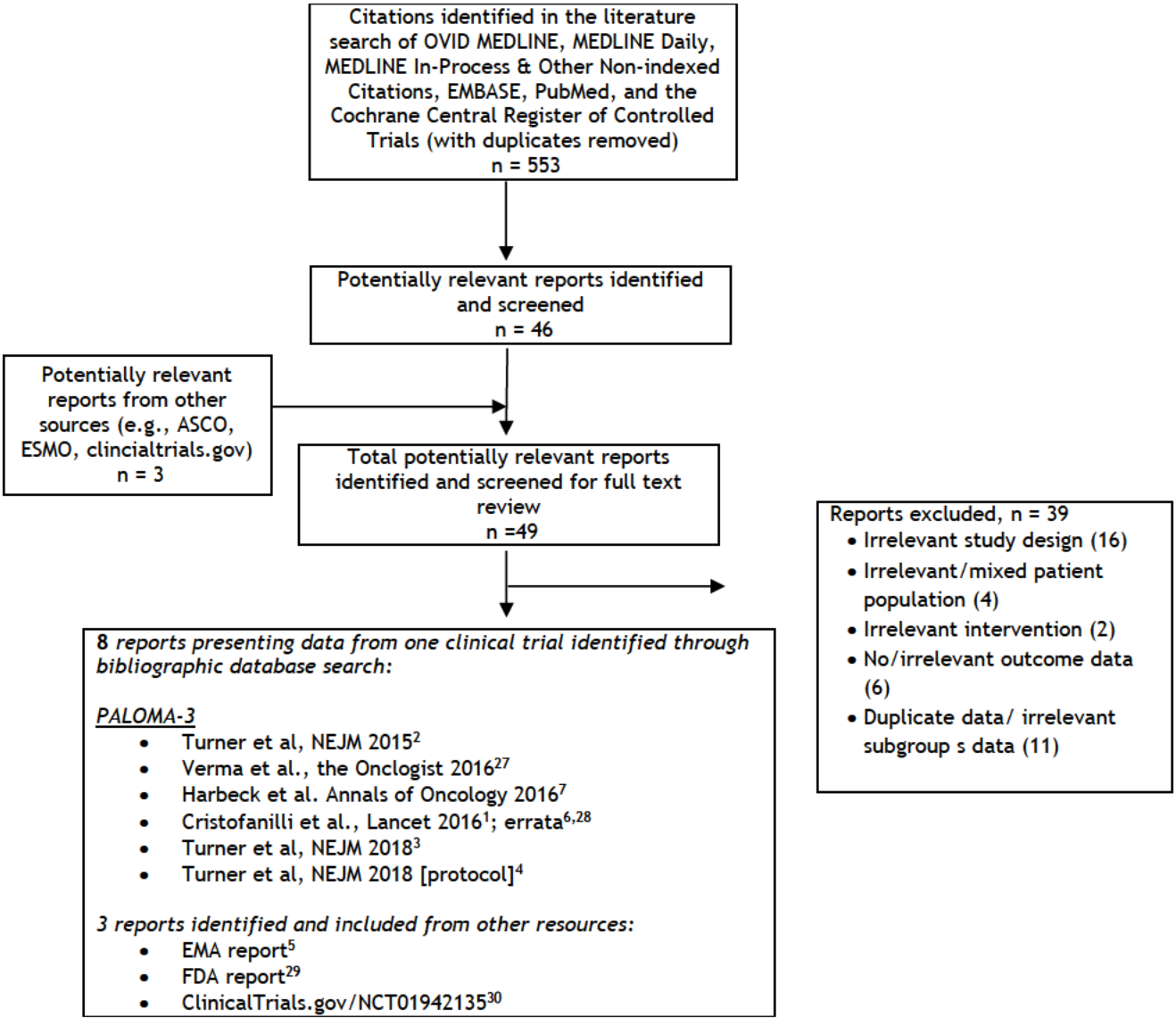
**Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*
***Defined as the sum of complete and partial response and stable disease for 24 weeks or more.*

6.3 Results

6.3.1 Literature Search Results

Of the 49 potentially relevant citations identified, 11 citations, reporting data from one clinical trial, were included in the pCODR systematic review,[1-7,27-30] and 39 citations were excluded. Studies were excluded because they were irrelevant study types,[31-46] did not use the intervention of interest,[47,48] included irrelevant or mixed patient population,[49-52] reported irrelevant outcome data,[8,53-55] Articles and conference abstracts reporting duplicate data from the included studies were also excluded.[26,56-63] Figure 6.1 illustrates the PRISMA flow Diagram for the study selection process.

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



Note: Additional data related to the PALOMA-3 trial were also obtained through requests to the Submitter by pCODR[10]

6.3.2 Summary of Included Studies

One randomized controlled trial (RCT) met the selection criteria of this review.

6.3.2.1 Detailed Trial Characteristics

PALOMA-3 was a phase 3, multicentre, randomized, double-blind, placebo controlled comparing (in a 2:1 ratio) palbociclib + fulvestrant with placebo plus fulvestrant (placebo + fulvestrant) in women with HR+, HER2-, locally ABC or mBC whose disease had progressed after prior endocrine therapy regardless of their menopausal status.[1-3] Relevant information on trial characteristics is 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 : PALOMA-3[1-4,7,27] NCT01942135[30] Characteristics: phase 3, multicentre, randomized, double-blind, placebo controlled, parallel group N= 521 randomized N= 517 treated Number of centres and number of countries: 144 centers in Canada, US, Belgium, Germany, Ireland, Italy, Netherlands, Portugal, Romania, Russian Federation, Turkey, Ukraine, UK, Australia, Japan, Republic of Korea, and Taiwan Patient enrolment dates 07-October-2013 to 26-August-2014 Data cut-off dates:† 05-December-2014 16-March-2015 23-October-2015 Final analysis date: 13-April-2018 Funding: Pfizer	<u>Key Inclusion Criteria:</u> • Women aged ≥18 years • pre-, peri, or post-menopausal • Histologically or cytologically proven diagnosis of breast cancer with evidence of metastatic or locally advanced disease, not amenable to curative resection or radiation therapy • Documented HR+ (protocol-defined) • Documented HER2-negative tumor (protocol-defined) • Progressed during or after previous endocrine therapy • Measurable disease as defined by RECIST v 1.1, or bone-only disease with a lytic or mixed lytic disease • ECOG PS of 0-1 <u>Key Exclusion Criteria:</u> • Prior treatment with CDK inhibitor, fulvestrant, everolimus, or a PI3K /mTOR pathway inhibitor • Extensive symptomatic visceral metastasis • Uncontrolled CNS metastases	<u>Intervention*</u> palbociclib (oral; 125 mg QD; 3 weeks on/1 week off) + fulvestrant (IM; 500 mg q4w) <u>Comparator*</u> Placebo + fulvestrant (IM; 500 mg q4w) *All pre- or peri-menopausal women were also treated with an LHRH agonist	<u>Primary:</u> • PFS <u>Secondary:</u> • OS • Survival probabilities at 1, 2, and 3 years • ORR • Duration of response • Clinical benefit <u>Quality of life</u> <u>Safety</u> • AEs • SAEs • Withdrawal due to AEs • Mortality

AE = adverse event; **CDK** = cyclin-dependent kinase; **ECOG PS** = Eastern Cooperative Oncology Group performance score;**HER2-** = human epidermal growth factor receptor 2 negative; **HR+** = hormone receptor positive; IM = intramuscular; **LHRH** = Luteinizing hormone-releasing hormone; **mTOR** = mechanistic target of rapamycin; **PFS** = progression-free survival; **ORR** = objective response rate; **OS**= overall survival, **PI3K** =phosphoinositide 3-kinase; **q4w** = every 4 weeks; **QD** = once a day; **RECIST** = Response evaluation criteria in solid tumors; **SAE** = serious adverse events; ; **UK** = United Kingdom; **US** = United States of America

†Data cut off dates by types of analyses: 05-December-2014 - primary PFS analysis and first interim analysis for OS; 16-March-2015 - updated (final) analysis for PFS; 23-October-2015 - updated analysis for PFS and formal interim analysis for OS;13-April-2018 - final OS analysis

Table 6.3: Select quality characteristics of included studies of [drug] in patients with [disease]

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
PALOMA-3	Palbociclib + fulvestrant vs placebo + fulvestrant	PFS	417	521	Stratified randomization	Yes centralized interactive web-/voice-based randomization	Yes Double-blind Placebo-controlled	Yes	Yes	Yes The trial stopped early (April 2015)for efficacy benefit	Yes

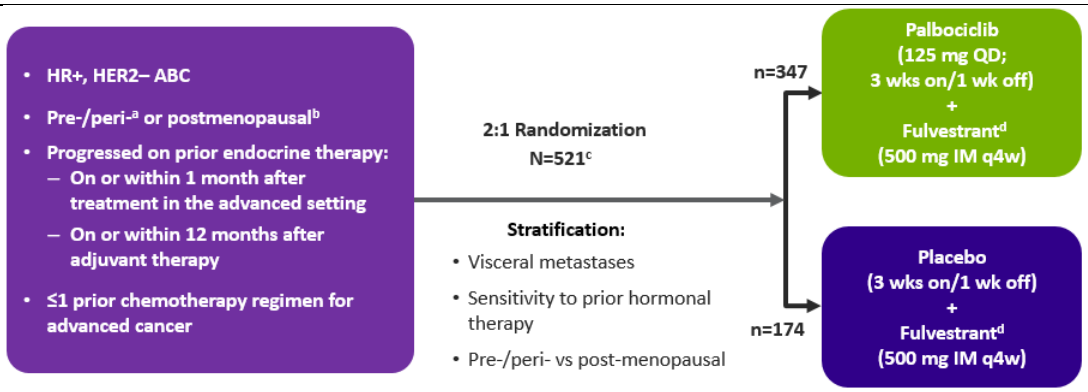
a) Trials

PALOMA-3 was a phase 3, international, multicenter, randomized, double-blind, placebo-controlled trial that compared the safety and efficacy of palbociclib + fulvestrant with placebo + fulvestrant in women with HR+, HER2-, locally ABC or mBC whose disease had progressed after prior endocrine therapy regardless of their menopausal status.[1-3] The trial was conducted at 144 sites in 17 countries: Australia (11 sites), Belgium (11 sites), Canada (11 sites), Germany (2 sites), Ireland (1 site), Italy (9 sites), Japan (8 sites), the Netherlands (6 sites), Portugal (2 sites), Romania (4 sites), the Russian Federation (5 sites), the Republic of South Korea (5 sites), Taiwan (2 sites), Turkey (1 sites), the Ukraine (6 sites), the United Kingdom (4 sites), and the United States (56 sites).[1,2]

Trial design

The study consisted of a pre-randomization phase, a randomization and treatment phase, and a post-treatment follow-up period.[4] At the baseline, patients were screened for eligibility. Informed consent was obtained and baseline data were collected on clinical and laboratory examinations, tumor assessment, and patient reported outcome measurements.[29] Eligible patients were randomized in a 2:1 ratio to receive palbociclib + fulvestrant or placebo + fulvestrant (28-day cycles). All pre- or peri-menopausal women were also treated with a LHRH agonist at least four weeks before randomization and received goserelin (an injectable LHRH agonist) at the time of the fulvestrant injection.[1,5] Post-baseline tumour assessments were performed (using CT, MRI or both) every 8 weeks (±7 days) for the first year, and every 12 weeks (±7 days) thereafter until radiographically and/or clinically documented disease progression according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1), discontinuation of the study treatment, initiation of new anticancer therapy, or patient withdrawal from study participation (death, patient's request, lost to follow-up).[4,5] The study design is illustrated in Figure 6.2.

Figure 6.2: Design of the PALOMA-3 trial



[a] All pre-/peri-menopausal patients received goserelin.
[b] Patients must have progressed on prior endocrine therapy (pre-/peri-menopausal) or AI therapy (postmenopausal).
[c] Number of patients randomized.
[d] Fulvestrant was administered on Days 1 and 15 of Cycle 1, then every 28th day.
Abbreviations: ABC = advanced breast cancer; AI = aromatase inhibitor; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; IM = intramuscular; q4w = every 4 weeks; QD = once daily; wk(s) = week(s).
Source: Cristofanilli et al., 2016.[1]

Source: [Pfizer Clinical Summary Figure 3.1 page 23][10]

Randomization and treatment concealment

Randomization was performed by the investigator or another designated member of the research team using a centralized interactive web-based and voice-based randomization system. Randomization was stratified based on three factors:

- sensitivity to previous hormonal therapy, defined as a documented clinical benefit from ≥ 1 previous endocrine therapy in the metastatic setting or treatment with ≥ 24 months of adjuvant therapy before disease recurrence;
- menopausal status at the baseline, i.e., postmenopausal vs premenopausal or peri menopausal; and
- presence of visceral metastases, i.e., lung, liver, brain, pleural, or peritoneal involvement.

Patients were randomized into palbociclib + fulvestrant or placebo + fulvestrant arms in a 2:1 ratio using permuted-block randomization with a block size of six for each of the stratification levels.[1,4,5]

Study participants, investigators, and research staff were blinded to the treatment assignment. Blinding codes could only be broken in emergency situations 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. However, representatives of the Sponsor who were involved in the study design and data analysis remained blinded to the treatment group assignment until the independent data and safety monitoring committee (IDMC) recommended stopping the study at the pre-planned interim analysis (05-December-2014).[1,4,5] Double-blinding was maintained after both the primary analysis and the interim analysis. Unblinding occurred, after a request from the investigator, in 12 (3%) patients in the palbociclib + fulvestrant arm and in 18 (10%) patients in the placebo + fulvestrant arm. Seven cases of unblinding in the palbociclib + fulvestrant arm and 17 cases in the placebo +fulvestrant arm occurred after disease progression.[3]

Study endpoints and disease assessment

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.[2] Key secondary efficacy endpoints included:

- overall survival (OS), defined as the time from randomization to death from any cause;
- survival probability at 1, 2, and 3 years;
- objective response, defined as complete response (CR) or partial response (PR) according to RECIST;
- duration of response, defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first;
- clinical benefit, defined as CR or PR or stable disease (SD) of ≥24 weeks duration.[1,2,6]

Tumor assessments were conducted according to local practice, and selection of imaging studies (e.g., MRI, CT) depended on treating physician and radiologist as per local practice. After approval of Amendment #3 (20-Oct-2015), RECIST version 1.1 was not mandatory to evaluate imaging studies or to confirm disease progression.[4] Tumor assessments were performed radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression, discontinuation of study treatment (both agents), initiation of new anticancer therapy, or discontinuation of patient from overall study participation (e.g., death, patient's request, lost to follow-up), whichever occurs first. A series of ≥ 2 incomplete or indeterminate disease assessments would result in censoring of the primary endpoint of PFS back to the time of the last full assessment that did not show progression.[4] Patients who discontinued study treatment for reasons other than radiographically and/or clinically documented disease progression continued to have tumor assessments during the follow-up visits every eight weeks for the first year, and every 12 weeks thereafter until disease progression, initiation of new anticancer therapy or withdrawal from study participation.[4]

For patients who discontinued the active treatment phase, data on survival and new anti-cancer therapy were collected every three months for the first nine months, then every 6 months from the last dose of investigational product. The follow-up period was to be concluded at the time of the final OS analysis.[4]

Patient-reported outcomes (PRO) were measured using health-related quality-of-life scores on the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D), the European Organisation for Research and Treatment of Cancer (EORTC), the Quality of Life Core Module (QLQ-C30), and the EORTC Breast Cancer Module (QLQ-BR23).[2,4,7]

Adverse events (AEs) were followed until 28 days after discontinuation of the study treatments (i.e., palbociclib/placebo or fulvestrant).[29] Safety measurements included the type, incidence, severity (as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.0), seriousness of AEs; the relationship of AEs to study medications; and any laboratory abnormalities.[2,27] Laboratory safety assessments were performed at baseline and on day 1 of each cycle.[27]

Assessment of tumor tissue biomarkers was also performed, including genes (e.g., PIK3CA mutations), proteins (e.g., quantitative expression of estrogen and progesterone receptors), and RNA expression.[1,4]

Statistical analysis

Sample size calculation

The sample size for PALOMA-3 trial was determined based on the results of a randomized Phase 2 trial assessing fulvestrant with or without dasatinib in postmenopausal patients with HR+ mBC previously treated with an aromatase inhibitor. In the phase 2 study, the median PFS was 5.3 months for the fulvestrant alone arm and 6.0 months for the combination arm. Based on these results, the median PFS for the control arm in the Paloma-3 trial was assumed to be 6.0 months (versus the alternative hypothesis that median PFS in the palbociclib group was longer than 6.0 months). An improvement of 56% to a median PFS of 9.38 months (corresponding to a hazard ratio [HR] of 0.64) was considered clinically meaningful. A total of 238 events were required to achieve 90% power to detect a HR=0.64 with a one-sided significance level of α=0.025.[1,4]

Assuming a non-uniform accrual accomplished over a period of about 14 months, data follow-up for approximately 20 months from the start of study randomization for final PFS analysis, and a non-uniform dropout with dropout rate of 25% at 18 months for PFS, a total sample size was estimated to be 417 patients (278 in the fulvestrant plus palbociclib arm and 139 in the placebo plus fulvestrant arm).[1,4]

Interim analyses and data cut-off dates

- A preplanned interim analysis (data cut-off date 05-December-2014) of the primary endpoint of PFS was performed after 195 events of disease progression or death had occurred.[2] The safety of the palbociclib + fulvestrant combination was also assessed at the interim analysis.[2] The efficacy boundary of PFS at the interim analysis was pre-specified using the Haybittle-Peto method;[64,65] and because the study crossed the pre-specified Haybittle-Peto efficacy stopping boundary (i.e., α = 0·00135), the IDMC recommended stopping the study early (in April 2015).Patient enrolment was completed before the IDMC's decision about the interim analysis was made.[1]
- An updated analysis of the primary endpoint (16-March-2015 data cut-off date) was performed, after 259 PFS events were reached among 521 patients, to support the results of initial interim analysis. However, because the updated analysis was conducted after the pre-defined stopping point, the results of this analysis were considered to be exploratory.[1]
- The second updated analysis of PFS (23-October-2015 data cut-off date) was considered to be the final PFS analysis per protocol in terms of number of observed events. A formal interim analysis of OS data was also performed at this data cut-off.[8,9]
- The planned final analyses of OS and safety analyses were performed at a cut-off date of 13-April-2018, with a median follow-up of 44.8 months and after 310 deaths had reached among 521 patients.[3]

Efficacy analyses

The primary and secondary efficacy endpoints were analysed based on the intention-to-treat (ITT) population. The ITT population included all randomized patients, with study drug assignment designated according to initial randomization.[4] Efficacy analyses were performed using the local radiologist's or investigator's tumor assessments as the primary data source. An independent third-party core imaging laboratory performed a blinded independent central review (BICR) of PFS data for a randomly selected subgroup (approximately 40%) of patients.[4] Additional analyses of objective response rate (ORR) and clinical benefit rate (CBR) were also performed based on the review of the blinded independent third-party core imaging laboratory.[4]

- PFS- The primary analysis of PFS was performed in ITT population using a stratified log-rank test stratified based on the presence or absence of visceral disease and sensitivity to prior endocrine therapy.[2] PFS time associated with each treatment arm was summarized using the Kaplan-Meier method, with CIs reported for the 25th, 50th and 75th percentiles of the event-free time. HR, and the corresponding 95% CI, were calculated using the Cox proportional hazards model.[4] PFS data was censored on the date of the last tumor assessment for patients who did not have objective tumor progression and those who did

not die while on study. Patients who did not have an evaluation of tumor response after randomization had their PFS time censored on the date of randomization (i.e., one day study participation). Patients who started a new anti-cancer therapy prior to documented disease progression were censored at the date of the last tumor assessment prior to the start of the new therapy. Patients with documentation of disease progression or death after an unacceptably long interval since the last tumor assessment (i.e., ≥2 incomplete or non-evaluable assessments) were censored at the time of last objective assessment that did not show disease progression.[4]

- OS -All randomized patients were considered evaluable for the OS analyses. In the absence of confirmation of death, survival time was censored to last date the patient was known to be alive. To control for potential impact of multiple testing on Type I error, OS was hierarchically tested for significance at the time of the PFS interim analysis (i.e., the OS analysis would not be conducted if the primary analysis for PFS was not statistically significant). The overall significance level for the efficacy analysis of OS was preserved at one-sided $\alpha = 0.025$.[4]The median overall survival, and the corresponding 95% CIs, were estimated using the Kaplan–Meier method. The comparison between the two treatment arms was made with the use of a one-sided log-rank test with stratification according to the same stratification factors as for the PFS analysis. HR for OS, and the corresponding 95% CI, were calculated using the Cox proportional hazards model.[4] For the final analysis of OS, the pre-specified significance threshold was a two-sided p-value of 0.047, which was adjusted for the planned interim analyses.[4]
- ORR- For each treatment arm, ORR was estimated by dividing the number of patients with an objective response (CR or PR) by the number of patients randomized to the respective treatment arm. ORR was compared between the two treatment arms using Cochran-Mantel-Haenszel test with the same stratification factors as for the PFS analysis.[4]
- Duration of response (DR) - Analysis of DR was performed for the subgroup of patients with an objective response (i.e., CR or PR).[4] DR data was censored on the date of the last tumor assessment on study for patients who did not have objective tumor progression and those who did not die due to any cause during the study time. Duration of response for the two treatment arms were summarized using Kaplan-Meier methods. The median event time and 95% CI for the median was provided for each arm.[4]
- CBR - For each treatment arm, CBR was estimated by dividing the number of patients with CR, PR, or SD ≥24 weeks by the number of patients randomized to the treatment arm. CBR comparison between the two treatment arms were performed using Cochran-Mantel-Haenszel test with the same stratification factors as for the PFS analysis.
- Subgroups analyses were conducted for PFS (investigator-assessed and BICR), OS, and ORR based on predefined stratification factors (the presence or absence of sensitivity to previous endocrine therapy, the presence or absence of visceral metastatic disease, and menopausal status) and demographic/prognostic factors including age, geographical region, race, performance status, line of therapy in metastatic setting, and biomarkers.[1,3,26,52,60]

The sensitivity analyses were also performed to investigate the influences of the following factors on the primary endpoint of PFS (investigator-assessed and BICR):[4]

•Analysis population- based on As-Treated population (i.e., all patients who received at least one dose of the study treatment, with treatment assignments designated according to actual study treatment received)

• Use of stratified statistical methods

• Stratification factors and covariates

• Disease assessment scheduling,

- Deviations in tumor lesion assessment
- Bone-only disease patients (three sensitivity analyses) based on:
  - considering the following patients as censored: patients with bone-only disease who had on study fractures, on study pain management (e.g., palliative radiation therapy or surgery), clinical worsening not objectively confirmed (≥ 2 point increase from baseline in ECOG performance score in two assessments) or change of therapy (censored at the date of prior tumor assessment with no disease progression)
  - considering the following patients as events: patients with bone-only disease who had on study fractures, on study pain management (e.g., palliative radiation therapy or surgery), clinical worsening not objectively confirmed (≥2 point increase from baseline in ECOG performance score in two assessments) or change of therapy
  - excluding bone-only disease patients from the analysis.

•Missing data - based on considering the following censored PFS data in the primary analysis as PFS: new anti-cancer treatment, lost to follow-up, consent withdrawal, medication error without associated AE.

• Potential investigator bias on tumour assessment - based on combining random sample BICR data and investigator assessed PFS (event) data.

Safety analysis

Safety analysis was based on the As-Treated population that included patients who received at least one dose of the study treatment (i.e., palbociclib/placebo or fulvestrant).[4] Descriptive analysis was used to summarize the maximum grade AEs on treatment using terms from the Medical Dictionary for Regulatory Activities (MedDRA). The risk difference between the two treatment arms for hematologic and non-hematologic events of interest was calculated, along with the respective 95% CIs, with no adjustment for multiplicity.[27]

Patient-reported outcomes analyses

The analyses of patient-reported outcomes included patients in the ITT population who had a baseline assessment and at least one post-baseline assessment before the end of study treatment.

The primary (pre-specified) analysis of patient-reported outcomes used a longitudinal mixed-effect random intercept random slope model to compare the two treatment groups, with the treatment, time, treatment by time, and baseline value as the covariates for the model. The analysis was conducted based on both the observed values and the changes from baseline for EORTC QLQ-C30 and QLQ-BR23 scales. Analysis of time to deterioration (TTD) in pain scores was also pre-specified. Deterioration was defined as an increase of at least 10 points from the baseline. The 10- point threshold was chosen based on previously established thresholds for minimal important differences from the perspective of the patient.[7]

Post hoc analyses of TTD in global health status/health-related quality of life were performed using the Kaplan–Meier approach to survival analysis the Brookmeyer and Crawley method for computing 95% CIs. TTD was compared between the two treatment groups using the log-rank test (one-sided; $\alpha = 0.025$). No adjustments were made for multiple comparisons.[7]

Protocol amendments[4]

There were three protocol amendments during the PALOMA-3 trial. A summary of the key changes are provided in Table 6.4:

Table 6.4 - Summary of the protocol amendments in the PALOMA-3 trial		
Protocol Amendment	Date	Key Changes
Amendment 1	04-April-2014	Revised the study drug administration instructions from administration of palbociclib in a fasted state to administration with food and to prohibit the concomitant use of proton-pump inhibitors
Amendment 2	30-September-2014	Prospectively characterized whether or not palbociclib affects glucose metabolism through monitoring of appropriate laboratory measurements given the nonclinical findings in rats and taking into account the limited laboratory glucose data in the current clinical dataset Added prospective monitoring of hemoglobin A1c to characterize whether or not palbociclib affected glucose metabolism Added clarification of adverse events follow-up procedure (telephone contact) at 28 calendar days after treatment discontinuation
Amendment 3	20-October-2015	Reduced some of the safety and efficacy assessments due to completion of efficacy analyses (i.e., interim and final analyses of primary and secondary endpoints), analyses of safety conducted to comply with Health Authorities requirements, and small number of patients remaining under observation in the study Clarified that, after approval of Amendment 3, survival follow-up visits would be conducted every 3 months, and tumor assessments would be conducted as per local practice (with no requirement for mandatory tumor assessment at the End of Treatment visit), selection of imaging studies would depend on treating physician and radiologist as per local practice, and RECIST version 1.1 would not be mandatory any longer to evaluate imaging studies nor to confirm disease progression.
Source: [PALOMA-3 Final protocol A5481023][4]		

b) Populations

Eligibility criteria[4]

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

- Histologically or cytologically proven diagnosis of breast cancer with evidence of metastatic or locally advanced disease, not amenable to resection or radiation therapy with curative intent.
- Documented estrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive tumor (≥1% positive stained cells) based on most recent tumor biopsy (unless bone-only disease) utilizing an assay consistent with local standards.
- Documented HER2-negative tumor based on local testing on most recent tumor biopsy HER2-negative tumor is determined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH/DISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4.
- Progressed during treatment or within 12 months of completion of adjuvant therapy with an aromatase inhibitor if postmenopausal, or tamoxifen if pre- or perimenopausal; or progressed while on or within one month after the end of prior aromatase inhibitor therapy for advanced/metastatic breast cancer if postmenopausal, or prior endocrine treatment for advanced/metastatic breast cancer if pre- or peri-menopausal. One

previous line of chemotherapy for advanced/metastatic disease is allowed in addition to endocrine therapy.
- Measurable disease as defined by RECIST v 1.1, or bone-only disease with a lytic or mixed lytic disease that could be accurately assessed by CT or MRI.
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1.
- Adequate organ and marrow function as defined by the study protocol.

Postmenopausal was defined by at least one of the following criteria:

- age ≥60 years;
- Age <60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and serum estradiol and follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females;
- Documented bilateral oophorectomy;
- Medically confirmed ovarian failure

Patients not meeting the criteria for being postmenopausal were considered to be Pre-/ peri-menopausal. PALOMA-3 included pre-/peri-menopausal women if amenable to be treated with the LHRH agonist goserelin. Patients were to have started treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to randomization. However, if patients had received an alternative LHRH agonist prior to study entry, they were to switch to goserelin for the duration of the study.

Patients were excluded from the study if they had:

- Previously received any CDK (cyclin-dependent kinase) inhibitor, fulvestrant, everolimus, or a PI3K (phosphoinositide 3-kinase)/mTOR (mechanistic target of rapamycin) pathway inhibitor
- Extensive symptomatic visceral metastasis and were at risk of life-threatening com plications in the short term
- Prior hematopoietic stem cell or bone marrow transplantation
- Any other malignancy within 3 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix
- Uncontrolled CNS metastases

Characteristics of the study population

Between 26 Sept 2013 and 26 Aug 2014, a total of 521 pre-/peri- and post-menopausal women were randomized (2:1) to receive palbociclib + fulvestrant arm (n=347) or placebo + fulvestrant arm (n= 174). Patients were enrolled from 17 countries, with 14% of patients recruited from Canada (29/347 [8%] in the palbociclib + fulvestrant arm and 10/174 [6%] in the placebo + fulvestrant arm).[2,5]

Baseline demographic and disease characteristics of the ITT population are presented in Table 6.5 and Table 6.6, respectively. As showed, the baseline demographic variables were well balanced between the study arms. The median age was 57 years (range 29 to 88), with the majority of patients being younger than 65 years of age (75.2%), White (73.9%), from non-Hispanic or non-Latino ethnicities (94.0%). A total of 77.9% of the patients had measurable disease, and 23.2% had at least partially lytic bone-only disease; 97.1% of patients were ER-positive and 69.1% were PR-positive.[2,5] Based on the results published by Turner et al (2015),[2] 67.0% of patients had both ER–positive and PR–positive disease, and 26.7% were ER-positive but PR– negative. The most commonly involved disease sites included bone (75.2%), liver (39.9%), and lymph nodes (38.6%). As described in Table 6.6, a larger proportion of patients in the palbociclib + fulvestrant arm had an ECOG performance score of 1 (40.3% versus 33.9% in the placebo + fulvestrant arm).

A description of the study population by the stratification factors used for randomization and analysis is provided in Table 6.7. Overall, the stratification factors were well balanced between arms. At the study entry (randomization), 20.7% of patients were pre-/peri-menopausal, and 79.3% were post-menopausal; 59.7% presented with visceral metastases and 78.7% had a documented sensitivity to prior hormonal therapies.[29] Overall, 67.4% of patients in the palbociclib + fulvestrant arm and 64.3% of those in the placebo + fulvestrant arm had ≥ 2 involved disease sites.[2,5]

Prior treatments were also well-balanced between the two study arms (Table 6.8); except, in the palbociclib group, a larger proportion of patients had undergone more than one prior hormonal therapy regimens for their primary diagnosis (61.7% versus 55.7% in the placebo + fulvestrant arm). In addition, a larger proportion of patients in the placebo + fulvestrant arm had received a previous chemotherapy regimen for their primary diagnosis (79.3% versus 72.3% in the palbociclib + fulvestrant arm).[5]

Table 6.5: Baseline characteristics of the PALOMA-3 study population

Demographic Parameters	Palbociclib plus Fulvestrant N=347 N (%)	Placebo plus Fulvestrant N=174 N (%)	Total N=521 N (%)
Sex			
Male	0	0	0
Female	347 (100)	174 (100)	521 (100)
Age			
Mean years (SD)	56.9 (11.7)	56.8 (10.4)	56.9 (11.3)
Median (years)	57	56	57
Min, max (years)	30-88	29-80	29-88
Age Group			
≥ 17 - < 65 years	261 (75.2)	131 (75.3)	392(75.2)
≥ 65 - < 75 years	59 (17.0)	37 (21.3)	96 (18.4)
≥ 75 years	27 (7.8)	6 (3.4)	33 (6.3)
Race			
White	252 (72.6)	133 (76.4)	385 (73.9)
Black or African American	12 (3.5)	8 (4.6)	20 (3.8)
Asian	74 (21.3)	31 (17.8)	105 (20.2)
Other	8 (2.3)	1 (0.6)	9 (1.7)
Ethnicity			
Hispanic or Latino	17 (4.9)	11 (6.3)	28 (5.4)
Not Hispanic or Latino	329 (94.8)	161 (92.5)	490 (94)

Source: Modified from Study 1023 CSR Table 15 and demog.xpt

Source:[FDA report; Table 11, page 54][29]

Table 6.6: Disease characteristics in the PALOMA-3 study population

	Palbociclib plus Fulvestrant N=347 N (%)	Placebo plus Fulvestrant N=174 N (%)	Total N=521 N (%)
Measurable disease			
Yes	268 (77.2)	138 (79.3)	406 (77.9)
No	79 (22.8)	36 (20.7)	115 (22.1)
Adequate baseline assessment			
Yes	346 (99.7)	174 (100)	520 (99.8)
No	1 (0.3)	0	1 (0.2)
Bone Only Disease			
Yes	84 (24.2)	37 (21.2)	121 (23.2)
ER Status			
Positive	339 (97.7)	167 (96.0)	506 (97.1)
Negative	1 (0.3)	2 (1.1)	3 (0.6)
Missing	7 (2.0)	5 (2.9)	12 (2.3)
PR Status			
Positive	243 (70.0)	117 (67.2)	360 (69.1)
Negative	91 (26.2)	48 (27.6)	139 (26.7)
Missing	13 (3.7)	9 (5.2)	22 (4.2)
HER2 status			
Positive	2 (0.6)	2 (1.1)	4 (0.8)
Negative	341 (98.3)	171 (98.3)	512 (98.3)
Equivocal	3 (0.9)	1 (0.6)	4 (0.8)
Missing	1 (0.3)	0	1 (0.2)
Histopathologic classification			
Ductal	233 (67.1)	106 (60.9)	339 (65.1)
Lobular	40 (11.5)	22 (12.6)	62 (11.9)
Other	74 (21.3)	46 (26.4)	120 (23.0)
Histologic Grade			
1	22 (6.3)	16 (9.2)	38 (7.3)
2	162 (46.7)	79 (45.4)	241 (46.3)
3	93 (26.8)	40 (23.0)	133 (25.5)
Stage at Initial Diagnosis			
I	26 (7.5)	13 (7.5)	39 (7.5)
II	120 (34.6)	56 (32.2)	176 (33.8)
III	69 (19.9)	47 (27.0)	116 (22.3)
IV	86 (24.8)	36 (20.7)	122 (23.4)
Other/Unknown	46 (13.3)	22 (12.6)	68 (13.1)
ECOG Performance Status			
0	207 (59.7)	115 (66.1)	322 (61.8)
1	140 (40.3)	59 (33.9)	199 (38.2)
Involved Disease Sites			
Bone	163 (75.8)	129 (74.1)	392 (75.2)
Breast	61 (17.6)	19 (10.9)	80 (15.4)
Liver	127 (36.6)	81 (46.6)	208 (39.9)
Lung	103 (29.7)	44 (25.3)	147 (28.2)
Lymph Node	138 (39.8)	63 (36.2)	201 (38.6)
Other	109 (31.4)	46 (26.4)	155 (29.8)

Source: Modified from Study 1023 CSR Table 16 demog.xpt, and othbas.xpt

Source: [FDA report; Table 12, pages 55-56][29]

Table 6.7: PALOMA-3 study population by stratification factors

	Palbociclib plus Fulvestrant N=347 N (%)	Placebo plus Fulvestrant N=174 N (%)	Total N=521 N (%)
Based on randomization:			
Visceral metastases			
Yes	206 (59.4)	105 (60.3)	311 (59.7)
No	141 (40.6)	69 (39.7)	210 (40.3)
Documented sensitivity to prior hormonal therapy			
Yes	274 (79.0)	136 (78.2)	410 (78.7)
No	73 (21.0)	38 (21.8)	111 (21.3)
Menopausal status			
Pre-/perimenopausal	72 (20.7)	36 (20.7)	108 (20.7)
Postmenopausal	275 (79.3)	138 (79.2)	413 (79.3)
Based on CRF:			
Visceral metastases			
Yes	206 (59.4)	105 (60.3)	311 (59.7)
No	141 (40.6)	69 (39.7)	210 (40.3)
Documented sensitivity to prior hormonal therapy			
Yes	273 (78.7)	133 (76.4)	406 (77.9)
No	74 (21.3)	41 (23.6)	115 (22.1)
Menopausal status			
Pre-/perimenopausal	71 (20.5)	36 (20.7)	107 (20.5)
Postmenopausal	276 (79.5)	138 (79.3)	414 (79.5)

Source: Study 1023 CSR Table 17

Source:[FDA report; Table 13, page 57][29]

Table 6.8: prior treatments received by the PALOMA-3 study population

	Palbociclib plus Fulvestrant N=347 n (%)	Placebo plus Fulvestrant N=174 n (%)	Total N=521 n (%)
Prior surgeries			
No	62 (17.9)	25 (14.4)	87 (16.7)
Yes	285 (82.1)	148 (85.1)	433 (83.1)
Not reported	0	1 (<1.0)	1 (<1.0)
Prior radiation therapies			
No	107 (30.8)	43 (24.7)	150 (28.8)
Yes	238 (68.6)	130 (74.7)	368 (70.6)
Not reported	2 (<1.0)	1 (<1.0)	3 (<1.0)
Prior systemic therapies			
No	0	0	0
Yes	347 (100)	174 (100)	521 (100)
Number of regimens			
1	71 (20.5)	39 (22.4)	110 (21.1)
2	106 (30.5)	56 (32.2)	162 (31.1)
3	98 (28.2)	35 (20.1)	133 (25.5)
>3	72 (20.7)	44 (25.3)	116 (22.3)
Not reported	0	0	0
Previous chemo regimen for primary diagnosis [1]			
No	96 (27.7)	36 (20.7)	132 (25.3)
Yes	251 (72.3)	138 (79.3)	389 (74.7)
Oncology treatment types			
Neoadjuvant	69 (19.9)	33 (19.0)	102 (19.6)
Adjuvant	151 (43.5)	91 (52.3)	242 (46.4)
Advanced/metastatic	107 (30.8)	63 (36.2)	170 (32.6)
Missing	1 (<1.0)	0	1 (<1.0)
Previous hormonal regimen for primary diagnosis			
1	133 (38.3)	77 (44.3)	210 (40.3)
>1	214 (61.7)	97 (55.7)	311 (59.7)
Prior tamoxifen [2]	211 (60.8)	104 (59.8)	315 (60.5)
Prior aromatase inhibitors	296 (85.3)	151 (86.8)	447 (85.5)

Abbreviations: ITT: intent-to-treat, N: number of patients, n: number of patients affected, WHO: World Health Organization

1. The site confirmed that TAC, at variance of what reported by WHO Drug classification, is the acronym of the combination of the following chemotherapeutic agents: Docetaxel, Doxorubicin and Cyclophosphamide. TAC was classified as Chemotherapy.
   Chemotherapies reported as 'PALLIATIVE' oncology treatment type are classified as 'ADVANCED/METASTATIC'.
2. Includes Tamoxifen and Tamoxifen citrate.

Source: [EMA report; Table 16, page 60/140][5]

c) Interventions

Treatment Dosing Schedule[2,4]

Patients were randomized to the following two treatment arms:

Patients in arm A (palbociclib + fulvestrant) received palbociclib 125 mg administered orally once daily for 21 days followed by 7 days off treatment for each 28-day cycle (Schedule 3/1) plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and every 28 days (+/-7 days) thereafter starting from Day 1 of Cycle 1.

Patients in arm B (placebo + fulvestrant) received placebo administered orally once daily for 21 days followed by 7 days off treatment for each 28-day cycle (Schedule 3/1) plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and every 28 days (+/-7 days) thereafter starting from Day 1 of Cycle 1.

Pre- and peri-menopausal women started receiving goserelin or an alternative LHRH agonist at least 4 weeks before study treatment start 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 objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first. Crossover between treatment arms was not allowed. However, patients could continue treatment as assigned at randomization beyond the time of RECIST-defined disease progression at the discretion of the investigator if that was considered to be in the best interest of the patient and as long as no new anticancer treatment was initiated. In addition, should palbociclib/placebo related toxicity mandate palbociclib/placebo discontinuation, patients could continue to receive fulvestrant alone.[4]

Dose modifications

Palbociclib or placebo doses could be reduced to 100 mg daily and 75 mg daily on 3/1 schedule, respectively, or to 75 mg on a 2- week on/2-week off (2/2) schedule. Dose modification for fulvestrant was not allowed.[4,27]

As of 16-March-2015, in the palbociclib + fulvestrant arm, 28% (95/345) of patients had one dose reduction (from 125 to 100 mg or from 125 mg directly to 75mg), and 6% (22/345) of patients had two dose reductions. Among patients who only had one dose-level reduction, the median time to the dose reduction was 57 (range: 27 to 293) days for 125mg to 100 mg reductions, and 36 (range: 29 to 85) days for 125mg to 75 mg reductions (3/1 or 2/2 schedules). Among patients who had two dose reductions, the median time to the first dose reduction (125mg to 100 mg) was 34 (range: 27 to 142) days and the median time to the second dose reduction (100mg to 75 mg).was 120 (range: 56 to 352) days.[27]

At the data cut-off date, 36% (123/345) of patients had dose delays and 54% (187/345) had dose interruptions. The median duration of a dose interruption and dose delay in the palbociclib arm was 6.0 days and 2.5 days, respectively.[27]

Concomitant and subsequent interventions

Overall, 95.9% of patients in the palbociclib plus fulvestrant arm and 96.5% of patients in the placebo plus fulvestrant arm received concomitant drug treatment during the study.[29] The most commonly used concomitant medications included: paracetamol (24.6% with palbociclib + fulvestrant versus 26.2% with placebo +fulvestrant), denosumab (21.7% with palbociclib + fulvestrant versus 20.3% placebo +fulvestrant), goserelin (20.0% with palbociclib + fulvestrant versus 20.3% placebo +fulvestrant), zoledronic acid (18.3% with palbociclib + fulvestrant versus 21.5% placebo +fulvestrant) and ergocalciferol (16.8% with palbociclib + fulvestrant versus 12.2% placebo +fulvestrant).[29] All peri/pre-menopausal patients used goserelin in addition to the study treatments.[2]

Concurrent radiotherapy or cancer-related surgery was not permitted throughout the duration of the active treatment phase of the study. Palliative radiotherapy was permitted for the treatment of painful bony lesions provided that the lesions were known to be present at the time of study entry and the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression.[4,29]

Subsequent systemic anticancer therapies used by patients in the PALOMA-3 study are summarized in Table 6.9. The time from randomization to the first use of chemotherapy after disease progression was reported to be 17.6 months (95% CI 15.2, 19.7) in the palbociclib + fulvestrant arm and 8.8 months (95% CI 7.3,12.7) in the placebo + fulvestrant arm (HR= 0.58; 95% CI, 0.47, 0.73; P<0.001).[3]

.Table 6.9: Subsequent systemic anticancer treatments in the PALOMA-3 trial

Table 1. Systemic Anticancer Therapies Received as First, Second, and Third or Greater Lines of Subsequent Treatment by More Than 10% of the Patients in Either Trial Group Who Discontinued the Intervention.*

Treatment	Palbociclib–Fulvestrant Group (N=347)			Placebo–Fulvestrant Group (N=174)		
	First Line	Second Line	Third Line or Greater	First Line	Second Line	Third Line or Greater
	number of patients (percent)					
Any†	248 (71)	182 (52)	131 (38)	140 (80)	113 (65)	85 (49)
Chemotherapy						
Any	138 (56)	133 (73)	121 (92)	87 (62)	76 (67)	76 (89)
Eribulin	7 (3)	13 (7)	42 (32)	3 (2)	11 (10)	29 (34)
Paclitaxel	31 (12)	39 (21)	42 (32)	31 (22)	18 (16)	28 (33)
Capecitabine	66 (27)	43 (24)	36 (27)	36 (26)	20 (18)	24 (28)
Doxorubicin	12 (5)	7 (4)	35 (27)	1 (1)	10 (9)	12 (14)
Vinorelbine	6 (2)	8 (4)	23 (18)	7 (5)	5 (4)	21 (25)
Gemcitabine	7 (3)	6 (3)	26 (20)	5 (4)	9 (8)	15 (18)
Cyclophosphamide	13 (5)	9 (5)	23 (18)	8 (6)	4 (4)	8 (9)
Carboplatin	5 (2)	6 (3)	19 (15)	1 (1)	5 (4)	7 (8)
Antihormonal agent						
Any	100 (40)	40 (22)	38 (29)	52 (37)	29 (26)	31 (36)
Exemestane	57 (23)	20 (11)	21 (16)	25 (18)	15 (13)	13 (15)
mTOR kinase inhibitor						
Any	40 (16)	17 (9)	20 (15)	21 (15)	12 (11)	13 (15)
Everolimus	40 (16)	17 (9)	20 (15)	21 (15)	12 (11)	13 (15)
CDK4/6 inhibitor‡						
Any	6 (2)	2 (1)	6 (5)	9 (6)	6 (5)	15 (18)
Palbociclib	4 (2)	2 (1)	5 (4)	7 (5)	6 (5)	13 (15)
Ribociclib	1 (<1)	0	1 (1)	2 (1)	0	1 (1)
Abemaciclib	1 (<1)	0	0	0	0	2 (2)

* Percentages in the first row were calculated on the basis of the number of patients in the intention-to-treat population. Percentages in the remaining rows were calculated on the basis of the number of patients who received any treatment after the discontinuation of the trial intervention (i.e., the values in the first row). The term mTOR denotes mammalian target of rapamycin.

† One patient with missing data or partial information about start and stop dates for all reported follow-up therapies was not included in this analysis.

‡ In the placebo–fulvestrant group, 27 patients received inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6) after disease progression: 3 patients received ribociclib only; 22 patients received palbociclib only, 2 of whom received palbociclib twice in combination with different endocrine therapies (24 counts in the table); and 2 patients received both palbociclib and subsequent abemaciclib (4 counts in the table).

Source: From N Engl J Med, Turner NC, et al., Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer, Volume 379 No.20, Page No. 1926-1936, Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society., Table 1[3]

d) Patient Disposition

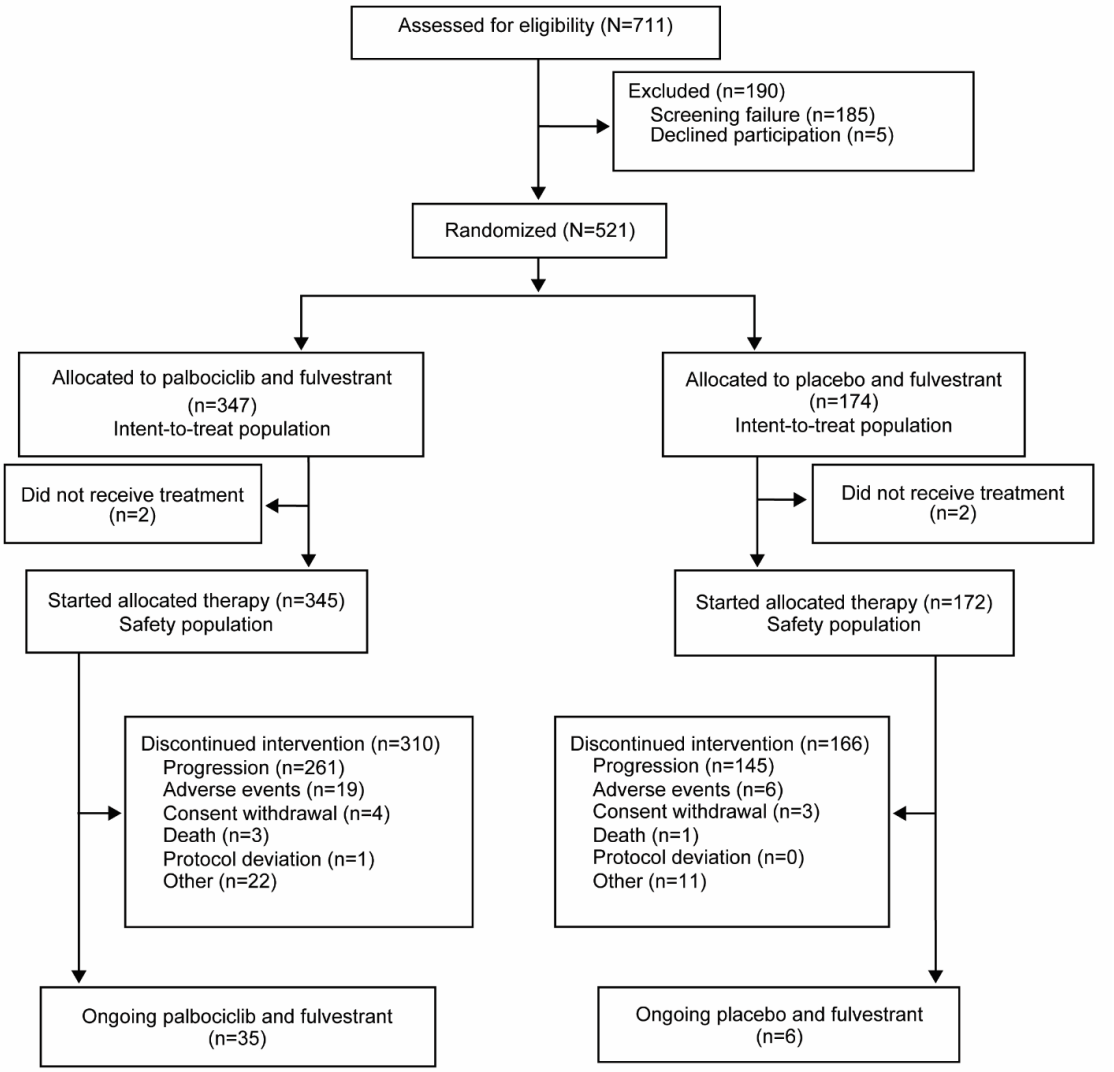
From September 26, 2013 to August 26, 2014, a total of 521 patients were randomized to receive palbociclib + fulvestrant (n=347) or placebo + fulvestrant (n=174).[2]

At the 05-December-2014 data cut-off date, 107 (30.8%) in the palbociclib + fulvestrant arm and 97 (55.7%) patients in the placebo + fulvestrant arm had discontinued study treatment, while 238 (68.6%) patients in the palbociclib + fulvestrant arm and 75 (43.1%) patients in the placebo + fulvestrant arm were still on study treatment. The most common reasons for study-treatment discontinuation included disease progression (24.5% of patients receiving palbociclib– + fulvestrant and 50.0% receiving placebo + fulvestrant), AEs (2.6% of patients receiving palbociclib– + fulvestrant and 1.7% receiving placebo + fulvestrant).[2,5]

At the longest follow up time (data cut-off of 13-April_2018), 310 (89.3%) in the palbociclib + fulvestrant arm and 166 (95.4%) patients in the placebo + fulvestrant arm had discontinued study treatment. A total of 35 (10.1%) patients in the palbociclib + fulvestrant arm and 6 (3.4%) patients in the placebo + fulvestrant arm continued to receive the study treatment (Figure 6.3). The most common reasons for study-treatment discontinuation included disease progression (75.2% of patients receiving palbociclib– + fulvestrant and 83.3% receiving placebo + fulvestrant), AEs (5.5% of patients receiving palbociclib– + fulvestrant and 3.4% receiving placebo + fulvestrant)[3]

Protocol violations/deviations
Overall, 69.5% of patients in each study arm were reported to have at least one protocol deviation. Major protocol deviations were reported in 125 (36%) patients in the palbociclib + fulvestrant arm and 51 (29.3%) patients in the placebo + fulvestrant arm. Major protocol deviations were mainly related to the inclusion/exclusion criteria (5.8% of palbociclib + fulvestrant and 7.5% in the placebo + fulvestrant arm), study drug administration/study treatment (21.0% in the palbociclib– + fulvestrant arm and 13.8% in the placebo + fulvestrant arm), informed consent 12.1% in the palbociclib– + fulvestrant arm and 5.7% in the placebo + fulvestrant arm), disallowed medication (4.6% of palbociclib– + fulvestrant and 6.3% in the placebo + fulvestrant arm), and AEs (1.4% of palbociclib– + fulvestrant and 0.6% in the placebo + fulvestrant arm).[29]

Figure 6.3: CONSORT diagram - PALOMA-3 trial



Data cut-off date13-April-2018

Source: [From N Engl J Med, Turner NC, et al., Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer, Volume 379 No.20, Page No. 1926-1936, Supplement, Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; Figure S1[4]

Limitations/Sources of Bias

Overall, PALOMA-3 is 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 of all study outcomes; study participants, investigators, and research staff were blinded to the treatment assignment. Representatives of the Sponsor who were involved in the study design and data analysis remained blinded to the treatment group assignment until the time of the pre-planned interim analysis (05-December-2014).[1,4,5] Double-blinding (study participants, researchers) was maintained after both the primary analysis and the interim analysis.
- Allocation concealment was performed through a centralized interactive web-based and voice-based randomization system.
- A 2:1 randomization ratio was used to increase the probability that eligible patients would be randomized to receive palbociclib + fulvestrant, and to increase feasibility.
- A stratified randomization procedure based on known prognostic factors (i.e., sensitivity to previous hormonal therapy, menopausal status at the baseline, and presence of visceral metastases), and block randomization (with a block size of six for each of the stratification levels) were used to minimize potential imbalances between the study groups that might lead to biased results. The treatment arms were well-balanced for patient characteristics and prognostic factors.
- Analyses of efficacy endpoints were based on radiographic tumor assessments by the investigators. An independent third-party core imaging laboratory performed a blinded independent central review of PFS data for a randomly selected subgroup (approximately 40%) of patients. Additional analyses of ORR and CBR were also performed based on the review of a blinded independent third party core imaging laboratory.
- Data analysis included an ITT analysis (i.e., patients were analyzed according to the groups to which they were originally assigned), which provides more conservative estimates of effect. Two patients in each arm did not receive the intervention to which they were randomized.
- To control for potential impact of multiple testing on Type I error, OS was hierarchically tested for significance at the time of the PFS interim analysis, and the overall significance level for the efficacy analysis of OS was preserved at one-sided $\alpha = 0.025$.
- Sensitivity analyses were performed to investigate the influences of factors such as analysis population, stratification factors, disease assessment scheduling, missing data, and investigator bias (see section 6 for more details).

Limitations

- PALOMA-3 compared the effect of palbociclib + fulvestrant with that of placebo + fulvestrant. Other comparators that are potentially relevant to this review were not assessed in this trial (i.e., aromatase inhibitors, selective estrogen receptor modulators, and chemotherapy). Of note, the submitter provided an indirect treatment comparison (ITC) report that included other endocrine therapies as comparators (see section 7 for more details). In the submitted ITC report, the submitter confirmed that the starting point for their indirect comparisons was a broad systematic review conducted by Pfizer global that included both endocrine therapies and chemotherapies. However, the report

submitted to pCODR excluded the results related to chemotherapies. During the pCODR Review Team meetings, the Clinical Guidance Panel (CGP) noted that in practice the majority of potentially eligible patients are post-menopausal women in whom chemotherapy would not be a very relevant therapy. Therefore, no indirect comparisons of palbociclib + fulvestrant versus chemotherapy were presented in this pCODR review.

- The PALOMA-3 trial stopped early for efficacy benefit. In interpreting evidence from trials that stopped early for apparent benefit, the likelihood of substantial overestimates of effect should be taken into consideration, especially in trials with fewer than 500 events.[66,67]
- It was noted in the study protocol that the sample size described above would allow the assessment of differences in the secondary endpoint of OS. However, in their manuscript reporting the results of long-term OS analysis,[4] Turner et al noted that finding a threshold for significant prolongation of OS in the context of a disease in which survival after disease progression is substantially longer than the time in the trial was challenging. The authors suggested that in order to detect a significant improvement in OS (HR = 0.80), an 80% power calculation would involve more than 700 events, as compared to the PALOMA-3 trial that achieved approximately 46% power to detect a HR = 0.80, with 310 deaths among the 521 patients at the time of OS analysis.[3]
- Although the subgroup analyses were pre-specified, subgroup analyses in the PALOMA-3 trial should be considered exploratory considering the fact that the study was not designed to detect differences in the specific subgroups.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Progression-Free Survival (PFS)

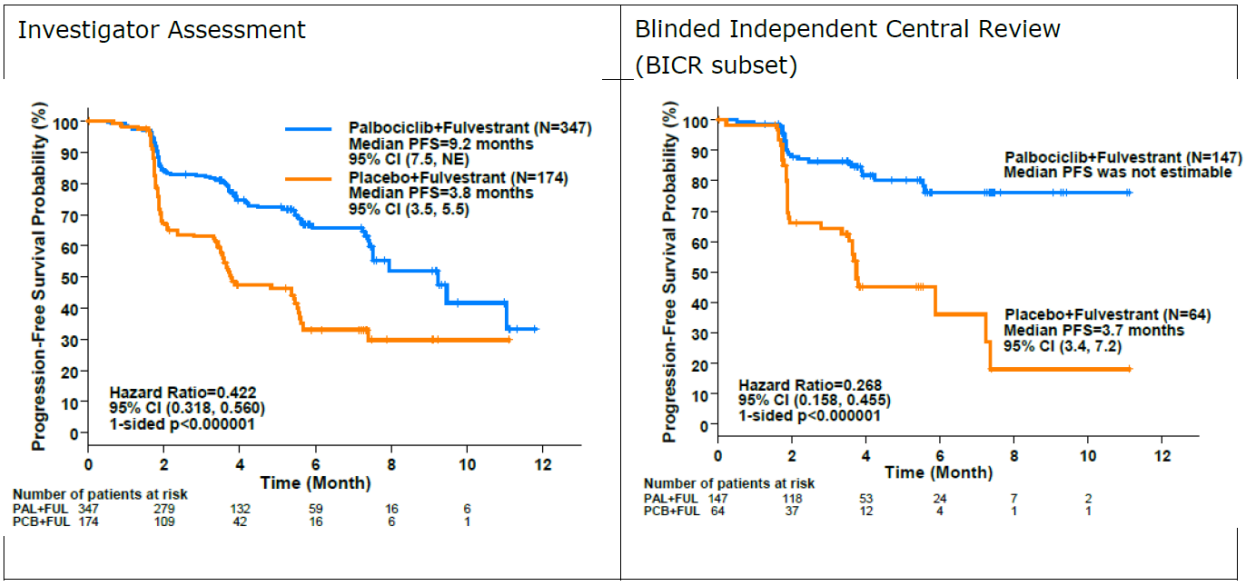
Investigator-assessed PFS (based on RECIST version 1.1) was the primary endpoint in the PALOMA-3 trial.

At the time of the pre-planned primary analysis (05-December-2014 data cut-off), after a median follow-up duration of 5.6 months,102 PFS events (29.3%) had occurred in the palbociclib + fulvestrant arm and 93 events (53.4%) in the placebo + fulvestrant arm. The median PFS was 9.2 months (95% CI, 7.5, not estimable) with palbociclib + fulvestrant and 3.8 months (95% CI 3.5, 5.5) with placebo + fulvestrant (HR= 0.42; 95% CI 0.32, 0.56; p <0.000001; Figure 6.4).[2,5] The results of the interim analysis crossed the pre-specified Haybittle-Peto efficacy boundary of α=0.00135; therefore, the study was stopped early (in April 2015) for efficacy (i.e., statistically significant prolongation in PFS).[1]

The results of the blinded audit, conducted on a random sample of approximately 40% of patients, were consistent with the results of the interim analysis. In the analysis of the BICR subset, the median PFS was not estimable with palbociclib + fulvestrant and was 3.7 months (95% CI 3.4, 7.2) in the placebo + fulvestrant arm (HR= 0.27; 95% CI, 0.16 to 0.46; P<0.001) (Figure 6.4).[2,5]

At the time of the first updated analysis (16-March-2015 data cut-off), after a median follow -up duration of 8.9 months, 145 PFS events (41.8%) had occurred in the palbociclib + fulvestrant arm and 114 events (65.5%) in the placebo + fulvestrant arm.[1] As of 23-October-2015 (second updated and final analysis for PFS), after a median follow-up of 15.8 months for patients in the palbociclib + fulvestrant arm and 15.3 months for those in the placebo + fulvestrant arm, a total of 333 PFS events (63.9%) had occurred: 200 events (57.6%) in the palbociclib + fulvestrant arm and 133 events (76.4%) in the placebo + fulvestrant arm. The median PFS was 11.2 months (95% CI 9.5, 12.9) with palbociclib + fulvestrant versus 4.6 months (95% CI 3.5, 5.6) with placebo + fulvestrant (HR = 0.497; 95% CI 0.398, 0.620; p<0.0001).[8]

Figure 6.4: Progression-free survival in the PALOMA-3 trial (ITT population; primary analysis)



Data cut-off date: 05-December-2014

Source: [EMA report; Figure 9, page 62/140][5]

Subgroup and sensitivity analyses of PFS

Subgroup analyses of PFS based on the pre-specified stratification factors and demographic or prognostic factors are shown in Figure 6.5. As shown, the results of the subgroup analyses were generally consistent with the results of the primary analysis; PFS benefit was reported in subgroup analyses based on the pre-specified stratification factors, i.e., the relative difference in PFS between the palbociclib + fulvestrant and placebo + fulvestrant arms was similar between:[2,26]

- Patients with documented sensitivity to previous endocrine therapy (HR = 0.39; 95% CI 0.28, 0.53) and those without sensitivity to previous endocrine therapy (HR = 0.55; 95% CI 0.31, 0.98; P = 0.88 for treatment-subgroup interaction)
- Patients with visceral metastatic disease (HR = 0.45; 95% CI 0.32, 0.63) and those without visceral metastatic disease (HR = 0.36; 95% CI 0.22, 0.60; P = 0.30 for treatment-subgroup interaction)
- Pre-or peri-menopausal patients (HR = 0.44; 95% CI 0.23, 0.83) and post-menopausal patients (HR = 0.41; 95% CI 0.30, 0.56; P = 0.94 for treatment-subgroup interaction)

However, in the following subgroups, there were no statistically significant difference in PFS between the palbociclib + fulvestrant and placebo + fulvestrant arms: patients with ≤24 months disease-free interval at baseline, patients with ≥3 previous lines of anticancer therapy in metastatic setting, and non-White ethnic subgroups (i.e., Asian, Black, and other).[2] It should be noted that the study was not powered to detect PFS benefit in the subgroups. Therefore, these subgroup analyses should be considered as exploratory.

The pre-specified sensitivity analyses of PFS which were performed to test the influence of the analysis population, use of stratified statistical methods, stratification factors and covariates, disease assessment scheduling, deviations in tumor lesion assessment, patients with bone-only disease, missing data, and investigator bias supported the primary efficacy endpoint results. In all of the sensitivity analyses HR remained stable around 0.4, indicating robustness of the PFS results.[5,29]

Figure 6.5: Progression-Free Survival in the PLAOMA-3 trial (by subgroups)

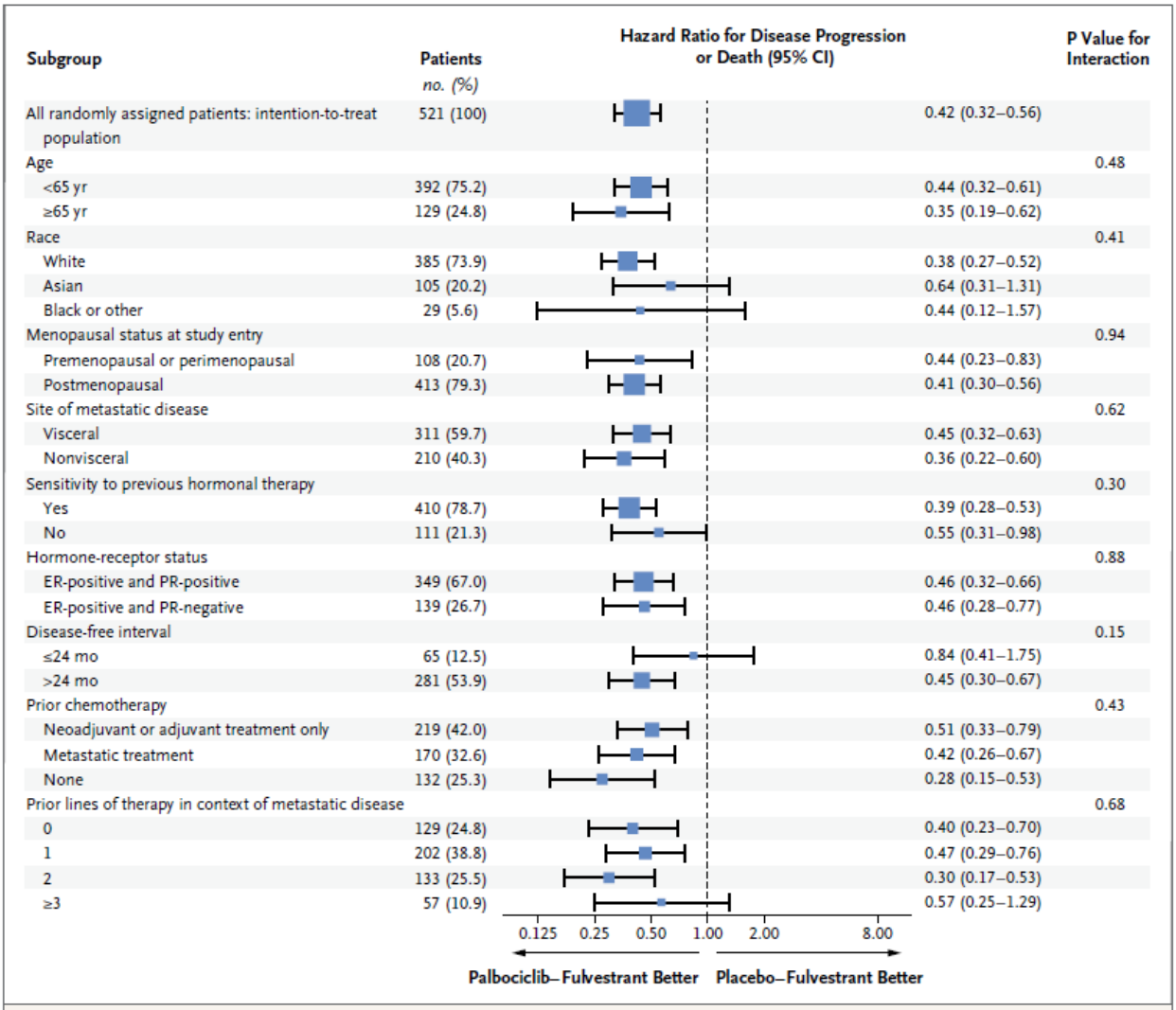


Figure 2. Subgroup Analysis of Progression-free Survival.
The blue boxes represent the hazard ratios with 95% confidence intervals (horizontal lines); the size of each box is proportional to the size of the corresponding subgroup. ER denotes estrogen receptor, and PR progesterone receptor.

Source:[From N Engl J Med, Turner NC, et al., Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer, Volume 373 No.3, Page No. 209-219, Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; Figure 2][2]

Overall Survival (OS),

OS was a key secondary endpoint in the PALOMA-3 trial. At the time of the interim analysis, after a median follow-up duration of 5.6 months, data on overall survival were immature, with 19 deaths (5.5%) in the palbociclib +fulvestrant arm and 9 deaths (5.2%) in the placebo + fulvestrant arm.[2]

The OS data were analyzed after a median follow-up duration of 44.8 months (13-April-2018 data cut-off) and after the data reached a 60% maturity (i.e., 310 deaths among 521 patients). At the data-cut-off date, 201 deaths had occurred in the palbociclib + fulvestrant arm and 109 deaths in the placebo + fulvestrant arm. The median OS was 34.9 months (95% CI 28.8, 40.0) for patients in the palbociclib + fulvestrant arm and 28.0 months (95% CI 23.6, 34.6) for those in the placebo + fulvestrant arm (stratified HR= 0.81; 95% CI, 0.64, 1.03; P = 0.09) (Figure 6.6A).[3] The OS rate at 3 years was estimated to be 50% (95% CI 44%, 55%) in the palbociclib + fulvestrant arm and 41% (95% CI 33%, 48%) in the placebo + fulvestrant arm.[3]

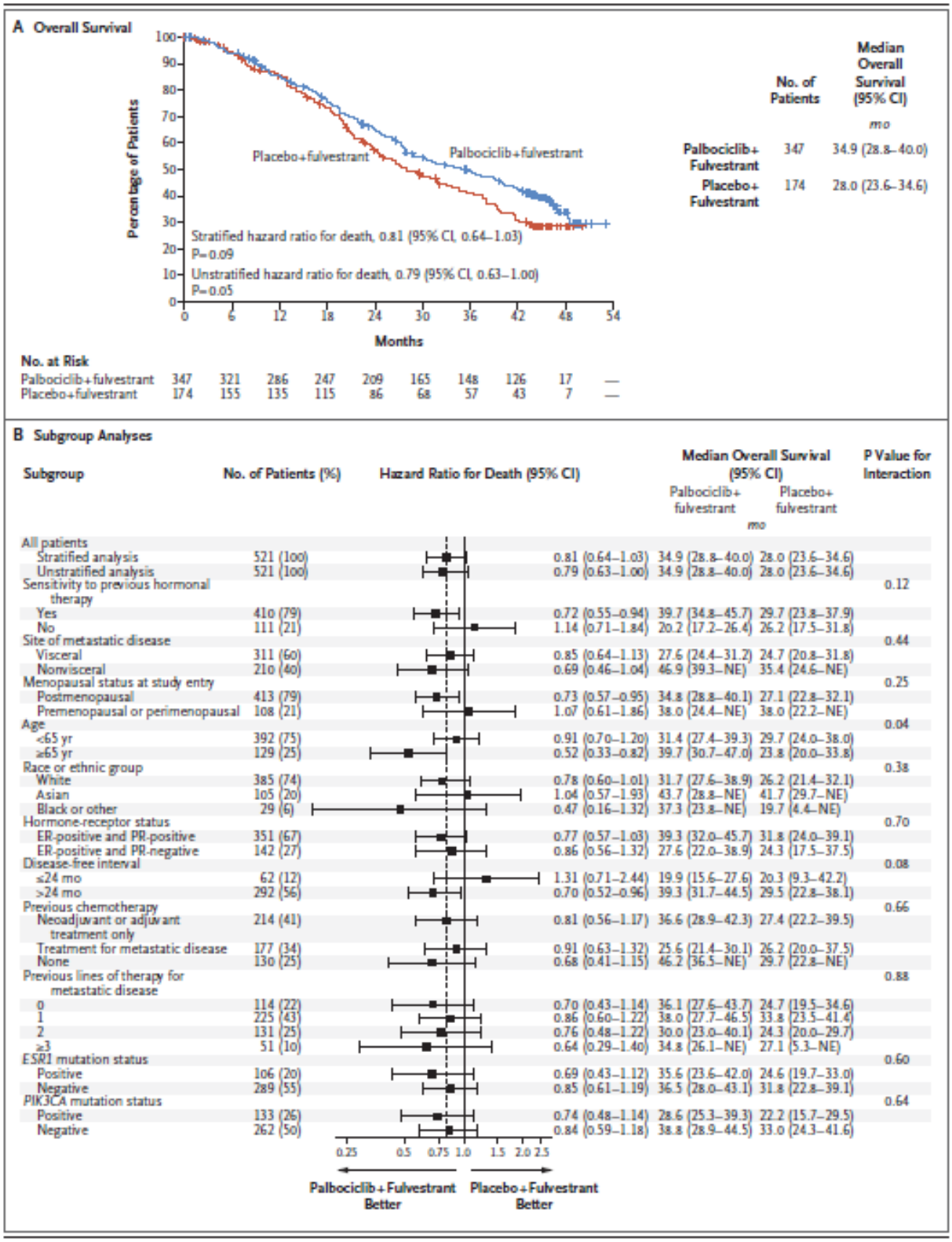
Subgroup analyses of OS

Subgroup analyses of OS are shown in Figure 6.6B. Results of subgroup analyses based on the pre-specified stratification factors were as follows:[3]

- Sensitivity to previous endocrine therapy - in patients with documented sensitivity to previous endocrine therapy, the median OS was 39.7 months for the palbociclib + fulvestrant arm and 29.7 months in the placebo + fulvestrant arm (absolute difference 10 months; HR = 0.72; 95% CI 0.55. 0.94); whereas, in patients without documented sensitivity to previous endocrine therapy, the median OS was 20.2 months for the palbociclib + fulvestrant arm and 26.2 months for the placebo + fulvestrant arm (absolute difference -6 months; HR = 1.14; 95% CI 0.71, 1.84). Test for treatment-subgroup interaction was not statistically significant (P = 0.12).
- Visceral metastatic disease - in patients with visceral metastatic disease, the median OS was 27.6 months for the palbociclib + fulvestrant arm and 24.7 months (for the placebo + fulvestrant arm (absolute difference 2.9 months; HR = 0.85; 95% CI 0.64, 1.13); while in patients without visceral metastatic disease, the median OS was 46.9 months in the palbociclib + fulvestrant arm and 35.4 months in the placebo + fulvestrant arm (absolute difference 11.5 months; HR = 0.69; 95% CI 0.46, 1.04). Test for treatment-subgroup interaction was not statistically significant (P = 0.44).
- Menopausal status - in postmenopausal patients, the median OS was 34.8 months for the palbociclib + fulvestrant arm and 27.1 months for the placebo + fulvestrant arm (absolute difference 7.7 months; HR = 0.73; 95% CI 0.57, 0.95); whereas, in pre- or peri-menopausal patients, the median OS was 38.0 months for both the palbociclib + fulvestrant and the placebo + fulvestrant arms (HR = 1.07; 95% CI 0.61, 1.86) Test for treatment-subgroup interaction was not statistically significant (P = 0.25).

It should be noted that the study was not powered to detect OS benefit in the subgroups. Therefore, these subgroup analyses should be considered as exploratory.

Figure 6.6: Overall Survival in the PLAOMA-3 trial (ITT population, and by subgroups)



Source: [From N Engl J Med, Turner NC, et al., Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer, Volume 379 No.20, Page No. 1926-1936, Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; Figure 1][3]

Objective Response Rate (ORR)

ORR was a secondary endpoint in the PLAOMA-3 trial. ORR results are shown in Table 6.10.

As of the 05-December-2014 data cut-off date, after a median follow-up duration of 5.6 months, ORR was reported to be 10.4% (95% CI 7.4, 14.1) in the palbociclib + fulvestrant arm and 6.3% (95% CI 3.2, 11.0) in the placebo + fulvestrant arm (P = 0.16).[2]

At the 16-March-2015 data cut-off date, after a median follow-up duration of 8.9 months, ORR was 19% (95% CI 15.0%, 23.6%) in the palbociclib + fulvestrant arm and 9% (95% CI 4.9%, 13.8%) in the placebo + fulvestrant arm. (p=0·0019).[1] For patients with measurable disease at baseline, ORR was 24.6% (95% CI 19.6%, 30.2%) in the palbociclib + fulvestrant arm and 10.9% (95% CI 6.2%, 17.3%) in the placebo + fulvestrant arm (p=0·0012).[1]

Clinical Benefit Rate (CBR)

CBR was a secondary endpoint in the PALOMA-3 trial and was defined as response (CR or PR) or prolonged stable disease (≥24 weeks) according to the RECIST version 1.1. CBR results are shown in Table 6.10.

As of the 05-December-2014 data cut-off date, CBR was 34.0% (95% CI 29.0, 39.3) in the palbociclib + fulvestrant arm and 19.0% (95% CI 13.4, 25.6) in the placebo + fulvestrant arm. The CBR difference between the two arms was statistically significant (P<0.001).[2]

As of the 16-March-2015 data cut-off date, CBR was 67% (95% CI 61.3%, 71.5%) in the palbociclib + fulvestrant arm and 40% (95% CI 32.3, 47.3) in the placebo + fulvestrant arm.[1] For patients with measurable disease at baseline, CBR was reported to be 64% (95% CI 57·7%, 69·6%) in the palbociclib + fulvestrant arm and 36% (95% CI 28.2%, 44.8%) in the placebo + fulvestrant arm (p<0.0001).[1]

Duration of Response (DOR)

DOR was a secondary endpoint in the PALOMA-3 trial. By the time of the first updated efficacy analysis (16-March-2015 data cut-off date), DOR was 9.3 months (95% CI not reported) in the palbociclib + fulvestrant arm and 7.6 months (95% CI not reported) in the placebo + fulvestrant arm.[29] at the time of the second updated analysis (23-October-2015 data cut-off date), DOR was reported to be 10.4 months (95% CI 8.3, not estimable) in the palbociclib + fulvestrant arm and 9.0 months (95% CI 5.6, not estimable) in the placebo + fulvestrant arm.[9]

Table 6.10: summary of selected secondary endpoints of the PALOMA-3 trial (ITT population and patients with measurable disease at baseline)

Outcome	Palbociclib + Fulvestrant	Placebo + Fulvestrant
All randomized patients, n	347	174
CR, n (%)	0 (0%)	4 (2%)
PR, n (%)	66 (19%)	11 (6%)
SD, n (%)	213 (61%)	94 (54%)
PD, n (%)	58 (17%)	57 (33%)
Indeterminate, n (%)	10 (3%)	8 (5%)
Objective response rate[a], % (95% CI)	19% (15-23.6)	9% (4.9-13.8)
Odds Ratio (95% CI); p value	2.47 (1.36-4.91); p = 0.0019	
Clinical benefit rate[b], % (95% CI)	67% (61.3-71.5)	40% (32.3-47.3)
Odds Ratio (95% CI); p value	3.05 (2.07-4.61); p < 0.0001	
Patients with measurable disease, n	268	138
CR, n (%)	0 (0%)	4 (3%)
PR, n (%)	66 (25%)	11 (8%)
SD, n (%)	143 (53%)	65 (47%)
PD, n (%)	51 (19%)	52 (38%)
Indeterminate, n (%)	8 (3%)	6 (4%)

Objective response rate[a], % (95% CI)	25% (19.6-30.2)	11% (6.2-17.3)
Odds Ratio (95% CI); p value	2.69 (1.43-5.26); p = 0.0012	
Clinical benefit rate[b], % (95% CI)	64% (57.7-69.6)	36% (28.2-44.8)
Odds Ratio (95% CI); p value	3.10 (1.99-4.92); p < 0.0001	

[a] Objective response was defined as a complete response (CR) or partial response (PR) according to RECIST criteria.
[b] Clinical benefit was defined as a complete response (CR) or partial response (PR) or stable disease (SD) for a duration of ≥24 weeks.
Abbreviations: CI = confidence interval; CR = complete response; ITT = intention to treat; PD = progressive disease; PR = partial response; SD = stable disease.
Source: Cristofanilli et al., 2016.[20]

Source:[Pfizer's IBRANCE™ (palbociclib) Clinical Summary, Table 3.4 pages28-29][10]

Quality of Life/patient-reported outcomes

PROs were evaluated in a subset of ITT patients, who had completed a baseline and at least one post-baseline PRO assessment prior to end of study treatment. As mentioned earlier in the trial design sub-section, PROs were evaluated using the instruments, EORTC QLQ-C30 (and its breast cancer module (EORTC QLQ-BR23) and EQ-5D.

From baseline to cycle 14, ≥96.9% of patients in the palbociclib + fulvestrant arm and ≥95.8% of patients in the placebo + fulvestrant arm completed ≥1 question on the EORTC QLQ-C30 questionnaire; ≥93.8% of patients in the palbociclib + fulvestrant arm and ≥95.8% of those in the placebo + fulvestrant arm completed ≥1 question on the EORTC QLQ-BR23.[7]

Global quality of life (QoL)

At the baseline, the mean scores for global QoL were similar between the palbociclib + fulvestrant (65.9; 95% CI 63.5, 68.2) and placebo + fulvestrant arms (65.3; 95% CI 61.9, 68.6). On treatment, the global QoL score was significantly higher in the palbociclib + fulvestrant arm (66.1; 95% CI 64.5, 67.7) than in the placebo + fulvestrant arm (63.0; 95% CI 60.6, 65.3; P = 0.0313)(Figure 6.7). Patients in the palbociclib + fulvestrant arm were also reported to have a significantly greater delay in deterioration of QoL, when compared to those in the placebo + fulvestrant arm (HR = 0.641; 95% CI 0.451, 0.910; P = 0.0065)(Figure 6.8).

Functional scales (QLQ-C30)

At the baseline, the mean scores for all five QLQ-C30 functional scales were similar between the palbociclib + fulvestrant and placebo + fulvestrant arms, with high functioning levels in both arms. Change from baseline scores for emotional functioning was statistically different between the palbociclib + fulvestrant arm (2.7; 95% CI 1.1, 4.3) and the placebo + fulvestrant arm (−1.9; 95% CI −4.2, 0.5; P = 0.0016), favoring palbociclib + fulvestrant. The overall changes from baseline scores were not statistically different between the two treatment arms for physical, role, cognitive, and social functioning (Figure 6.7).

Symptom scales (QLQ-C30)

At the baseline, the mean scores for symptoms of the EORTC QLQ-C30 were similar between the two study arms for all symptoms except insomnia (26.3 with palbociclib + fulvestrant versus 32.9 with placebo + fulvestrant). Baseline symptom scores were on the lower end of the 0–100 score range, indicating low symptom severity in both study arms.

Change from baseline scores for the EORTC QLQ-C30 symptoms are illustrated in Figure 6.9A. When compared to the placebo + fulvestrant arm, patients in the palbociclib + fulvestrant arm experienced statistically significant reductions in pain from baseline (−3.3 (95% CI −5.1, −1.5) versus 2.0 (95% CI −0.6, 4.6); P = 0.0011), and significantly less deterioration from baseline in nausea/vomiting (1.7 [95% CI 0.4–3.0] versus 4.2 [95% CI 2.3–6.1]; P = 0.0369).[7] The overall

changes from baseline scores were not statistically different between the two treatment arms for any other EORTC QLQ-C30 symptoms (Figure 6.9A).

TTD in pain was estimated to be 8 months (95% CI 5.6, not estimable) in the palbociclib + fulvestrant arm and 2.8 months (95% CI 2.3, 5.4) in the placebo + fulvestrant arm ([HR = 0.642; 95% CI 0.487, 0.846; P < 0.001)(Figure 6.8B).[7]

Functional scales (QLQ-BR23)

Figure 6.9B illustrates between-group differences in changes from baseline for the QLQBR23 functional scale scores. As shown, no significant differences were reported between the two study arms in overall change from baseline scores for any of the breast cancer specific functional scales.

Symptom scales (QLQ-BR23)

Figure 6.9C illustrates between-group differences in changes from baseline for the QLQ-BR23 symptom scale. Significantly greater deterioration from baseline was observed in the palbociclib + fulvestrant arm for upset by hair loss (2.9 [95% CI −1.7, 7.4] versus −6.0 [95% CI −12.3, 0.3] in the placebo + fulvestrant arm; P = 0.0255). No significant differences were reported between the two study arms for any of the other breast cancer-specific symptoms.

Similar PRO results were observed in a subgroup analysis of patients with visceral metastases.

Figure 6.7: Overall change from baseline in EORTC QLQ-C30 scores for global QoL and functional scales (PALOMA-3 PRO analysis population)

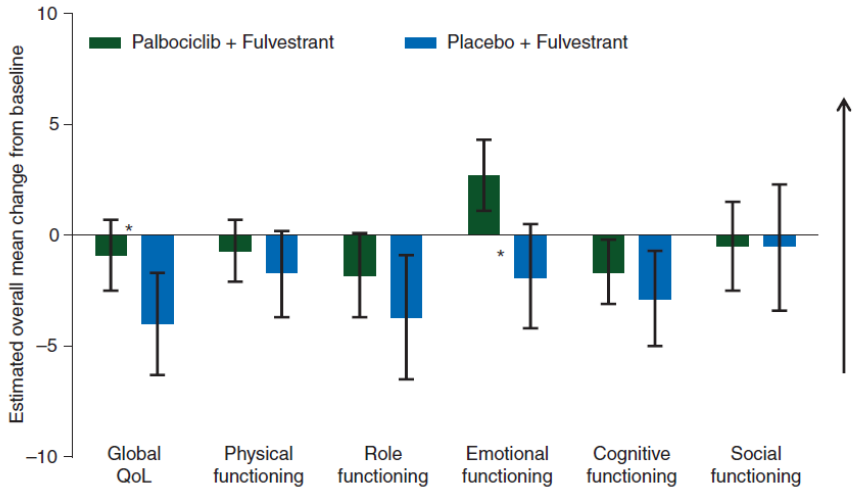


Figure 1. Overall change from baseline in EORTC QLQ-C30 scores for global QoL and functional scales in the PRO analysis set. Changes from baseline in the patient-reported outcomes analysis population were determined using a repeated-measures mixed-effect model. Arrow denotes direction of improved outcome; changes >0 indicate improvement from baseline. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; PRO, patient-reported outcomes; QoL, quality of life. Asterisks denote that the change from baseline was statistically significantly different between treatment groups.

Source: [Harbeck N, et al., Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial, Annals of Oncology, 2016, 27(6): p. 1047-54 by permission of European Society for Medical Oncology and Oxford University Press; Figure 1][7]

Figure 6.8. QLQ-C30: Deterioration in QoL and pain (PALOMA-3 PRO analysis population)

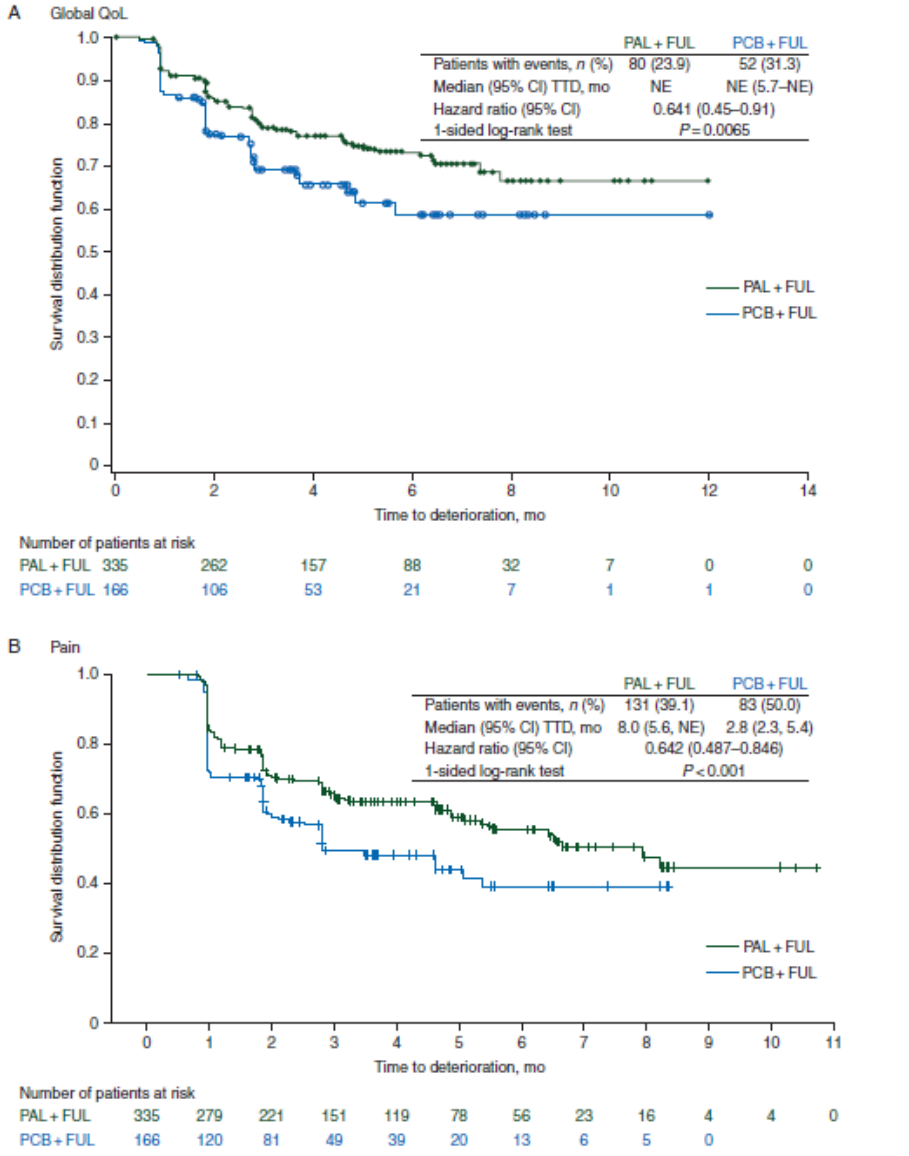


Figure 2. Time to deterioration in global QoL (A) and pain (B) in the PRO analysis set. Kaplan–Meier curves of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items (EORTC QLQ-C30) scores for the patient-reported outcomes analysis population. CI, confidence interval; NE, not estimable; TTD, time to deterioration; PRO, patient-reported outcomes; QoL, quality of life. Circles and pluses indicate patients censored.

Source: [Harbeck N, et al., Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial, Annals of Oncology, 2016, 27(6): p. 1047-54 by permission of European Society for Medical Oncology and Oxford University Press; Figure 2][7]

Figure 6.9: Changes from baseline in EORTC QLQ-C30 scores for symptom scales and EORTC QLQ-BR23 scores for functional) and symptom scales (PALOMA-3 PRO analysis population)

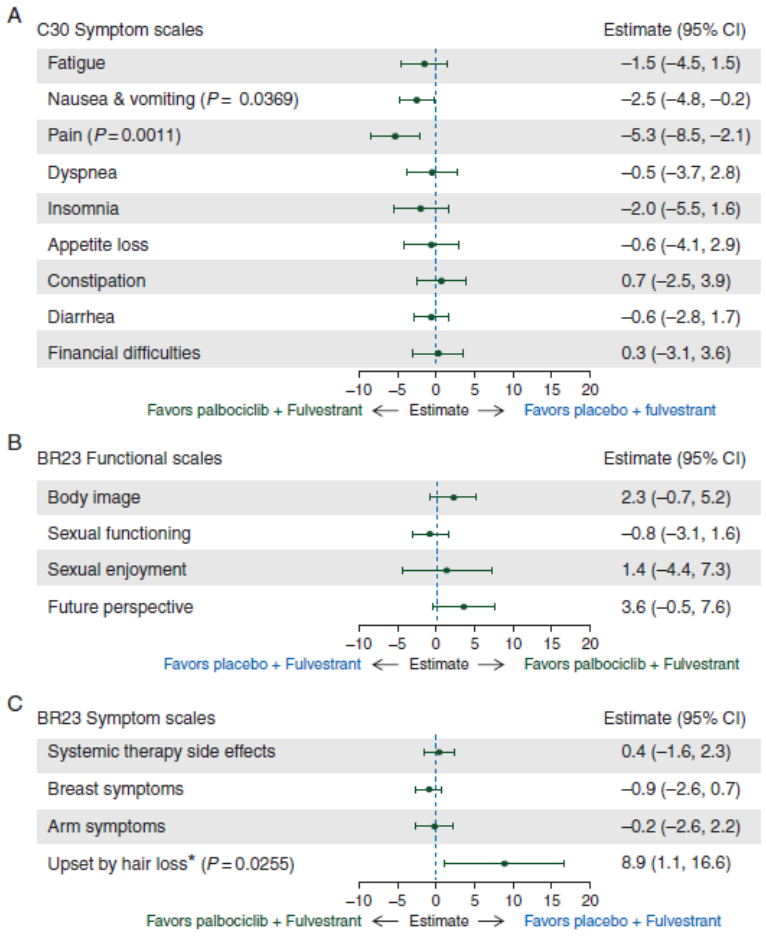


Figure 3. Between-treatment comparison of changes from baseline in EORTC QLQ-C30 scores for symptom scales (A) and EORTC QLQ-BR23 scores for functional (B) and symptom (C) scales in the PRO analysis set. Changes from baseline in the patient-reported outcomes analysis population were determined using a repeated-measures mixed-effect model. EORTC QLQ-BR23, European Organization for Research and Treatment of Cancer Breast Cancer Module; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; PRO, patient-reported outcomes; QoL, quality of life. *P* values are shown only if significant between-group differences were observed. Asterisk denotes that question was only to be answered by patients who stated they had experienced hair loss, resulting in fewer patients responding to this question compared with other questions.

Source: [Harbeck N, et al., Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial, Annals of Oncology, 2016, 27(6): p. 1047-54 by permission of European Society for Medical Oncology and Oxford University Press; Figure 3][7]

Harms Outcomes

Of the 521 patients enrolled in the PALOMA-3 trial, a total of 517 patients were treated (345 patients in the palbociclib + fulvestrant arm and 172 patients in the placebo + fulvestrant arm) and were included in the safety analysis (As-Treated population). A pre-planned safety analysis was performed at the time of the interim primary efficacy analysis (05-December-2014 data cut-off).[2] An updated analysis was performed at the 16-March-2015 data cut-off data, after a median follow-up of 8.9 months.[1,27] The final safety analyses was performed at the cut-off date of 13-April-2018, after a median follow-up of 44.8 months.[3]

Interim analysis

As of the 05-December-2014 data cut-off date, after a median follow-up of 5.6 months, 97.7% of patients in the palbociclib + fulvestrant arm and 89.0% of those in the placebo + fulvestrant arm had at least one reported AE (any grade) .The most common adverse events with palbociclib + fulvestrant group included neutropenia (78.8% versus 3.5% with placebo + fulvestrant), leukopenia (45.5% versus 4.1% with placebo + fulvestrant), fatigue (38.0% versus 26.7% with placebo + fulvestrant), nausea (29.0% versus 26.2% with placebo + fulvestrant), anemia (26.1% versus 9.9% with placebo + fulvestrant), and thrombocytopenia (19.4% versus 0% with placebo + fulvestrant).

Grade 3 or 4 AEs occurred in 69.3% of patients in the palbociclib + fulvestrant arm and 18.0% of those in the placebo + fulvestrant arm. The most common grade 3 or 4 AEs reported with palbociclib + fulvestrant included: neutropenia (62.0% versus 0.6% with placebo + fulvestrant), leukopenia (25.2% versus 0.6% with placebo + fulvestrant), anemia (2.6% versus 1.7%, with placebo + fulvestrant), and thrombocytopenia (2.3% versus 0% with placebo + fulvestrant). Febrile neutropenia occurred in two patients (0.6%) receiving palbociclib + fulvestrant and one patient (0.6%) receiving placebo + fulvestrant. A higher incidence of infections was reported in patients receiving palbociclib + fulvestrant (34.2%) than in patients receiving placebo + fulvestrant (24.4%), with upper respiratory infections being the most commonly reported infections (19.4% versus 16.3%).[2]

Serious AEs (any cause) occurred in 9.6% of the patients in the palbociclib + fulvestrant arm and 14.0% of the patients in the placebo + fulvestrant arm. Discontinuation of palbociclib (or matching placebo) due to AEs was reported in 2.6% of patients receiving palbociclib + fulvestrant and 1.7% of those receiving placebo + fulvestrant.[2] By the time of the primary analysis a total of six deaths had occurred: four deaths in the palbociclib + fulvestrant arm (all due to disease progression) and two deaths in the placebo + fulvestrant arm (one due to disease progression and one due to intracerebral hemorrhage).[2]

Final analysis

At the time of the long-term (final) safety analysis, the median number of cycles of therapy received was 12 (IQR 4, 21) in the palbociclib +fulvestrant arm and 5 (IQR 2, 12) in the placebo + fulvestrant arm. The results of the long-term analysis were consistent with those in the primary (interim) analysis. As shown in Table 6.11, neutropenia, infections, leukopenia, fatigue, nausea, and anemia remained the most commonly reported AEs.[3]

The most common grade 3 or 4 AEs reported in patients receiving palbociclib + fulvestrant were neutropenia (69.6% versus 0% with placebo + fulvestrant), and leukopenia (38.3% versus 5.8% with placebo + fulvestrant). Grade 3 anemia was reported in 4.3% of patients in the palbociclib + fulvestrant arm versus 2.3% of patients in the placebo + fulvestrant arm; and thrombocytopenia occurred in 2.9% of patients in the palbociclib + fulvestrant arm and 0% of patients in the placebo + fulvestrant arm. Febrile neutropenia was uncommon, (1% of the patients receiving palbociclib+ fulvestrant and in 0% of those in the placebo + fulvestrant arm.[3]

Based on the patient disposition diagram published by Turner et al (2018)(Figure 6.3), at the3-April-2018 data cut-off date, 19 (5.5%) patients in the palbociclib– + fulvestrant arm and 6 (3.4%) in the placebo + fulvestrant arm discontinued the study treatment due to AEs[3]

Table 6.11 : Summary of the final safety analysis in the PALOMA-3 trial

	Palbociclib + Fulvestrant (n=345)			Placebo + Fulvestrant (n=172)		
Adverse Event, n (%)	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Neutropenia*	290 (84.1)	200 (58.0)	40 (11.6)	6 (3.5)	0	0
Leukopenia†	207 (60.0)	129 (37.4)	3 (0.9)	9 (5.2)	1 (0.6)	0
Infections‡	188 (54.5)	15 (4.3)	3 (0.9)	60 (34.9)	6 (3.5)	0
Fatigue	152 (44.1)	9 (2.6)	0	54 (31.4)	2 (1.2)	0
Nausea	124 (35.9)	2 (0.6)	0	53 (30.8)	1 (0.6)	0
Anemia‖	109 (31.6)	15 (4.3)	0	24 (14.0)	4 (2.3)	0
Stomatitis§	104 (30.1)	3 (0.9)	0	24 (14.0)	0	0
Headache	99 (28.7)	3 (0.9)	0	37 (21.5)	0	0
Diarrhea	94 (27.2)	0	0	35 (20.3)	2 (1.2)	0
Thrombocytopenia¶	88 (25.5)	7 (2.0)	3 (0.9)	0	0	0
Cough	77 (22.3)	1 (0.3)	0	24 (14.0)	0	0
Constipation	76 (22.0)	0	0	28 (16.3)	0	0
Vomiting	75 (21.7)	2 (0.6)	0	28 (16.3)	1 (0.6)	0
Arthralgia	69 (20.0)	3 (0.9)	0	37 (21.5)	1 (0.6)	0
Alopecia	67 (19.4)	0	0	11 (6.4)	0	0
Back pain	66 (19.1)	5 (1.4)	0	34 (19.8)	3 (1.7)	0
Rash#	63 (18.3)	3 (0.9)	0	10 (5.8)	0	0

Decreased appetite	60 (17.4)	4 (1.2)	0	18 (10.5)	1 (0.6)	0
Pain in extremity	59 (17.1)	1 (0.3)	0	27 (15.7)	3 (1.7)	0
Dizziness	58 (16.8)	2 (0.6)	0	18 (10.5)	0	0
Hot flush	56 (16.2)	0	0	30 (17.4)	1 (0.6)	0
Dyspnea	48 (13.9)	1 (0.3)	1 (0.3)	16 (9.3)	2 (1.2)	0
Pyrexia	47 (13.6)	1 (0.3)	0	10 (5.8)	0	0
Insomnia	43 (12.5)	1 (0.3)	0	17 (9.9)	0	0
Musculoskeletal pain	43 (12.5)	1 (0.3)	0	16 (9.3)	1 (0.6)	0
AST increased	40 (11.6)	11 (3.2)	0	13 (7.6)	4 (2.3)	0
Dyspepsia	40 (11.6)	1 (0.3)	0	9 (5.2)	0	0
Edema peripheral	36 (10.4)	0	0	13 (7.6)	0	0
Muscle spasms	35 (10.1)	0	0	12 (7.0)	0	0
Myalgia	35 (10.1)	0	0	15 (8.7)	0	0

AST=aspartate aminotransferase; MedDRA=Medical Dictionary for Regulatory Activities.

*Neutropenia was categorized according to the MedDRA preferred terms neutropenia and neutrophil count decreased.

†Leukopenia was categorized according to the MedDRA preferred terms leukopenia and white blood cell count decreased.

‡Infections was categorized according to the MedDRA preferred term that is part of the System Organ Class infections and infestations.

§Anemia was categorized according to the MedDRA preferred terms anemia, hematocrit decreased, and hemoglobin decreased.

‖Stomatitis was categorized according to the MedDRA preferred terms aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, and stomatitis.

¶Thrombocytopenia was categorized according to the MedDRA preferred terms platelet count decreased or thrombocytopenia.

#Rash was categorized according to the MedDRA preferred terms dermatitis, dermatitis acneiform, rash, rash erythematous, rash maculopapular, rash papular, rash pruritic, and toxic skin eruption.

Source: [From N Engl J Med, Turner NC, et al., Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer, Volume 379 No.20, Page No. 1926-1936, Supplement, Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; Table S1][3]

6.4 Ongoing Trials

No ongoing trials were identified as being relevant to this review.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question were identified during development of the review protocol as relevant to the pCODR review of palbociclib + fulvestrant for HR+/HER2- locally advanced or metastatic breast cancer:

- Summary and critical appraisal of the systematic review and network meta-analysis comparing palbociclib with other therapies for HR+/HER2- Advanced or metastatic breast cancer patients whose disease progressed after prior endocrine therapy

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 systematic review and network meta-analysis comparing palbociclib with other therapies for HR+/HER2- advanced or metastatic breast cancer patients whose disease progressed after prior endocrine therapy

Given the absence of head-to-head trials against other currently funded therapies in Canada, the submitter provided an indirect treatment comparison (ITC) report comparing the efficacy of palbociclib with endocrine therapies in the second line treatment of patients with HR+/HER2– locally ABC or mBC.

During the protocol development phase, the review team had also identified chemotherapy agents as relevant comparators in this setting. In the submitted ITC report, the submitter confirmed that the starting point for their NMA was a broad systematic review conducted by Pfizer global that included both endocrine therapies and chemotherapies. However, the report submitted to pCODR excluded the results related to chemotherapies. During the pCODR Review Team meetings, the Clinical Guidance Panel (CGP) noted that in practice the majority of potentially eligible patients are post-menopausal women in whom chemotherapy would not be a very relevant therapy. Therefore, no indirect comparisons of palbociclib + fulvestrant versus chemotherapy agents are presented in this section.

Review of the submitted ITC[10]

7.1.1 Objective

The objective of the submitter-provided ITC was to indirectly compare the effect of palbociclib + fulvestrant with other available endocrine-based treatment options currently approved for the treatment of HR+/HER2– locally ABC or mBC after progression on endocrine therapy.

7.1.2 Methods

The submitted ITC was performed through conducting a systematic literature review and network meta-analysis (NMA).

Literature search and study selection

The submitter conducted a systematic review to identify eligible studies for the ITC. The literature search was built of a previously published systematic review by Wilson et al. (2017),[35] and updated the search to include relevant citations published between March 2016 and January

2018. The search was conducted in MEDLINE, Embase, Epub Ahead of Print, the Cochrane library, and conference proceedings from the American Society of Clinical Oncology (ASCO), American Association for Cancer Research (AACR), and European Society of Medical Oncology (ESMO). The search was designed to identify phase 2 and 3 randomized controlled trials (RCTs) comparing palbociclib + fulvestrant with endocrine therapies (anastrozole, exemestane, fulvestrant, letrozole, megestrol acetate, tamoxifen, everolimus + exemestane) for the treatment of women with HR+/HER2- locally ABC or mBC who have progressed after prior endocrine therapy.

Two reviewers independently selected studies and extracted data. The risk of bias assessment of eligible studies was extracted from Wilson et al. (2017). The assessment had been conducted using the National Institute for Health and Care Excellence (NICE) single technology appraisal checklist. Key outcomes of interest were PFS/time to progression (TTP) and OS.

ITC methodology

For each clinical outcome studied, a Bayesian NMA and pairwise meta-analyses were conducted to pool trial results when appropriate.

To reduce the risk of heterogeneity/inconsistency, the analysis was performed at the drug level (versus class level) and was stratified by individual doses of the various treatments of interest. Networks of drug comparisons for PFS/TTP and OS are illustrated in in Figure 7.1 and Figure 7.2, respectively. Within these networks, each drug is represented by a node and randomized comparisons between drugs are depicted by links between nodes. The size of the node is reflective of the sample size, and the width of the links is reflective of the number of studies connecting the treatment options.

For the NMA, both fixed effect and random effects models were conducted; however, it was noted in the submitter's report that the ability of the analysis to reliably estimate between-study variance was limited due to the large number of single-study connections in the network. Therefore, the submitter focused their report on findings from the fixed effect model but the results of the random effects model was also provided in an appendix. Model goodness of fit was assessed through comparing the posterior residual deviance from each NMA to the corresponding number of unconstrained data points.

To assess heterogeneity in the included studies, relevant study and patient characteristics (e.g., investigator versus central assessment of PFS, adjusted versus unadjusted hazard rations [HRs], percentages of HR+ and HER2- patients, blinding of studies, accounting for cross-over, etc.) were summarized and sensitivity analyses were conducted where possible. According to the submitter's report, meta-regression analyses or subgroup/sensitivity analyses related to certain characteristics of interest was not possible due to the presence of several single study connections between interventions.

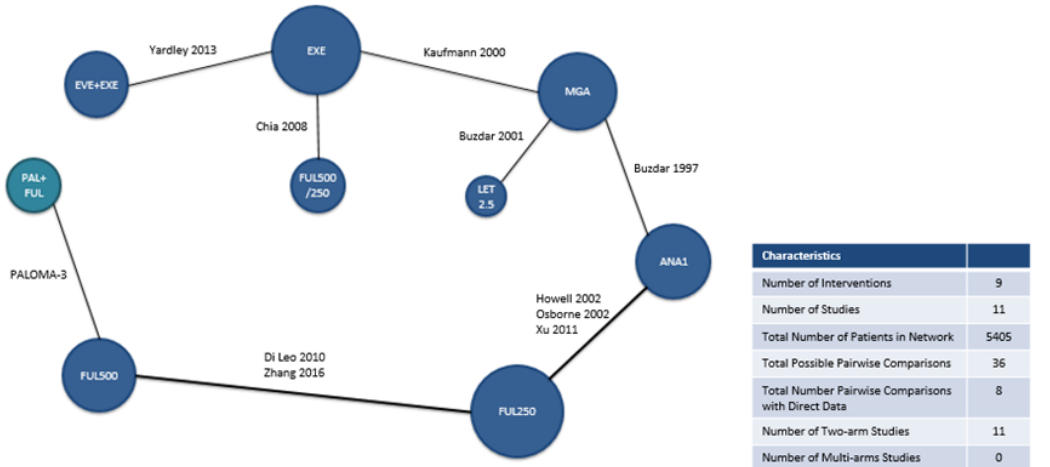
To assess inconsistency, deviance and deviance information criterion (DIC) statistics were compared (and plotted) in fitted consistency and inconsistency models. The results of the NMA were also qualitatively compared with pairwise estimates generated from direct evidence or traditional meta-analyses.

The proportional hazard assumption for the PALOMA 3 data was tested and confirmed by the submitter using the time-varying coefficient model.[9] However, the submitter stated that they were unable to confirm if the proportional hazards assumption had been formally tested and met for all of the studies included in the network meta-analysis; and that they had not attempted to digitize the Kaplan-Meier curves to reconstruct the patient-level data in order to assess the proportional hazard assumption, due to lack of clarity and lower resolution of related images, especially for older publications.[9]

While in some rare instances, NMA's analyze whole survival curves based on digitized KM curves, this approach becomes challenging when older publication (e.g. Buzdar et al. 1997, Buzdar et al.

2001) are included in the network, as the figures reported in those studies are generally lower resolution image-based formats that render the accuracy and precision of the reconstruction of patient-level data questionable.

Figure 7.1: Evidence network for PFS/TTP

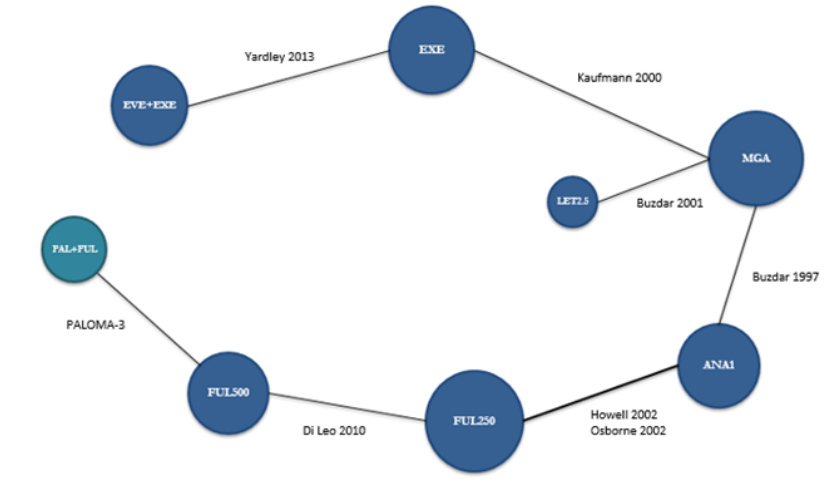


Characteristics	
Number of Interventions	9
Number of Studies	11
Total Number of Patients in Network	5405
Total Possible Pairwise Comparisons	36
Total Number Pairwise Comparisons with Direct Data	8
Number of Two-arm Studies	11
Number of Multi-arms Studies	0

Abbreviations: ANA1 = anastrozole 1 mg; EVE = everolimus; EXE = exemestane; FUL250 = fulvestrant 250 mg; FUL500 = fulvestrant 500 mg; LET2.5 = letrozole 2.5 mg; MGA = megestrol acetate; PAL = palbociclib; PFS = progression free survival; TTP = time to progression.

Source: [ITC submitted by Pfizer (04.03_Ibrance_Appendix A mBC progressed after prior endocrine therapy NMA.docx), Figure 3.2][10]

Figure 7.2: Evidence network for OS



Characteristics	
Number of Interventions	8
Number of Studies	8
Total Number of Patients in Network	4257
Total Possible Pairwise Comparisons	28
Total Number Pairwise Comparisons with Direct Data	7
Number of Two-arm Studies	8
Number of Multi-arms Studies	0

Abbreviations: ANA1 = anastrozole 1 mg; EVE = everolimus; EXE = exemestane; FUL250 = fulvestrant 250 mg; FUL500 = fulvestrant 500 mg; LET2.5 = letrozole 2.5 mg; MGA = megestrol acetate; OS = overall survival; PAL = palbociclib.

Source: [ITC submitted by Pfizer (04.03_Ibrance_Appendix A mBC progressed after prior endocrine therapy NMA.docx), Figure 3.3][10]

7.1.3 Findings

The search identified 11 studies for inclusion in the ITC. The list of the included studies is provided in Table 7.1. These studies evaluated the efficacy and safety of the following nine endocrine therapies: anastrozole 1 mg; exemestane 25 mg; fulvestrant 250 mg; fulvestrant 500 mg; fulvestrant 250/500mg; letrozole 2.5 mg; megestrol acetate 160 mg; everolimus 10 mg + exemestane 25 mg and palbociclib 125 mg + fulvestrant 500 mg. Of the 11 RCTs identified that met inclusion criteria, all studies reported data for PFS/TTP and eight reported data for OS.

Across the included studies, 47% to 100% of patients had a confirmed HR+ status, but HER2 receptor status was only reported in two studies. The proportion of patients receiving prior endocrine therapy in the advanced setting varied widely across studies from 10.2% to 89.2%; and the proportion of patients receiving prior endocrine therapy in the adjuvant setting ranged from 37.7% to 97.3%.

Table 7.1: Studies included in the submitter's network meta-analysis

Author	Title	Year	Comparator 1	Comparator 2
Buzdar et al., 1997[68]	A Phase III Trial Comparing Anastrozole (1 and 10 Milligrams), a Potent and Selective Aromatase Inhibitor, with Megestrol Acetate in Postmenopausal Women with Advanced Breast Carcinoma	1997	ANA1	MGA
Buzdar et al., 2001[69]	Phase III, Multicenter, Double-Blind, Randomized Study of Letrozole, an Aromatase Inhibitor, for Advanced Breast Cancer Versus Megestrol Acetate	2001	LET2.5	MGA
Chia et al., 2008[70]	Double-Blind, Randomized Placebo-Controlled Trial of Fulvestrant Compared With Exemestane After Prior Nonsteroidal Aromatase Inhibitor Therapy in Postmenopausal Women With Hormone Receptor-Positive, Advanced Breast Cancer: Results From EFECT	2008	EXE	FUL 500/250
Cristofanilli et al., 2016[1]	Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomized controlled trial	2016	PAL+FUL	FUL500
Di Leo et al., 2010[23]	Results of the CONFIRM Phase III Trial Comparing Fulvestrant 250 mg With Fulvestrant 500 mg in Postmenopausal Women With Estrogen Receptor-Positive Advanced Breast Cancer	2010	FUL250	FUL500
Howell et al., 2002[71]	Fulvestrant, Formerly ICI 182,780, Is as Effective as Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing After Prior Endocrine Treatment	2002	FUL250	ANA1
Kaufmann et al., 2000[72]	Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: Results of phase III randomized, double-blind trial	2000	EXE	MGA
Osborne et al., 2002[73]	Double-Blind, Randomized Trial Comparing the Efficacy and Tolerability of Fulvestrant Versus Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing on Prior Endocrine Therapy: Results of a North American Trial	2002	FUL250	ANA1

Xu et al., 2011[74]	Fulvestrant 250 mg versus anastrozole for Chinese patients with advanced breast cancer: results of a multicentre, double-blind, randomised phase III trial	2011	FUL250	ANA1
Yardley et al., 2013[75]	Everolimus Plus Exemestane in Postmenopausal Patients with HR+ Breast Cancer: BOLERO-2 Final Progression-Free Survival Analysis	2013	EVE+EXE	EXE
Zhang et al., 2016[76]	Fulvestrant 500 mg vs. 250 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer: a randomized, double-blind registrational trial in China	2016	FUL500	FUL250

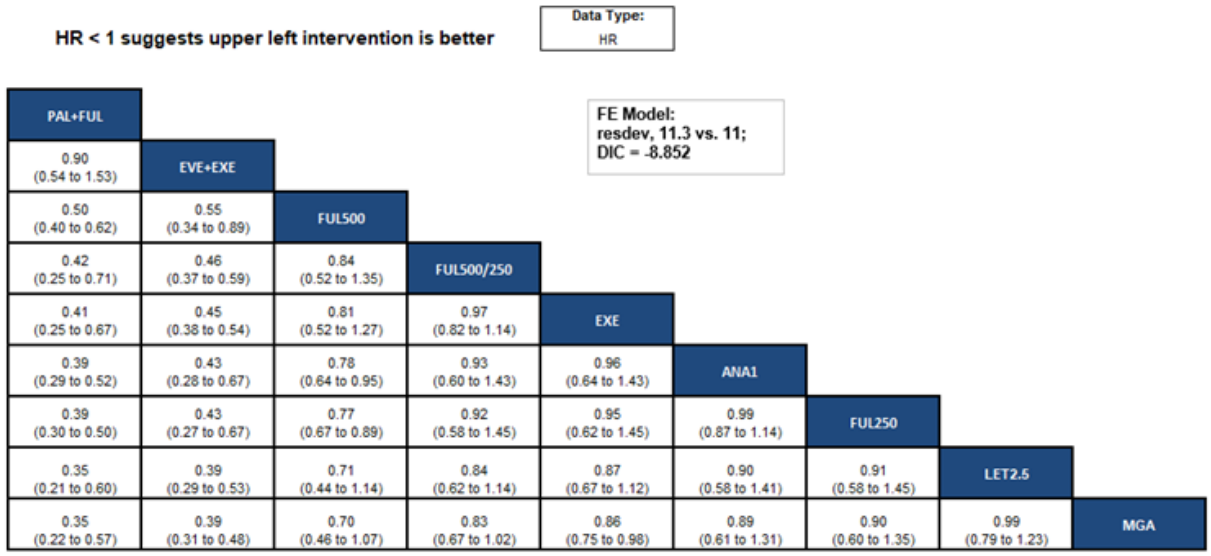
Abbreviations: ANA1 = anastrozole 1 mg; EVE = everolimus; EXE = exemestane; FUL250 = fulvestrant 250 mg; FUL500 = fulvestrant 500 mg; LET2.5 = letrozole 2.5 mg; MGA = megestrol acetate; PAL = palbociclib.

Source: [ITC submitted by Pfizer (04.03_Ibrance_Appendix A mBC progressed after prior endocrine therapy NMA.docx), Table 4.1][10]

Progression-Free Survival / Time to Progression

Results of the fixed effect NMA for PFS/TTP (Figure 7.3) showed that palbociclib + fulvestrant had superior efficacy (i.e., credible interval [CrI] did not cross 1) compared with each of the comparators except everolimus + exemestane for which no difference was found. These results were consistent with those found in the random effects NMA. In addition, the palbociclib + fulvestrant combination was associated with the highest probability of being the best treatment, with the highest Surface Under the Cumulative RAnking curve (SUCRA), and the best average rank for PFS/TTP.

Figure 7.3: Pairwise comparisons from the fixed effect NMA, PFS/TTP (reported as HRs with 95% CrIs)



Pairwise comparisons from the fixed effect model are shown in terms of summary HRs and 95% CrIs. Each value reflects a comparison between treatments belonging to the intersecting column and row, with additional benefit indicated for the treatment in the column. Model fit statistics are also presented.

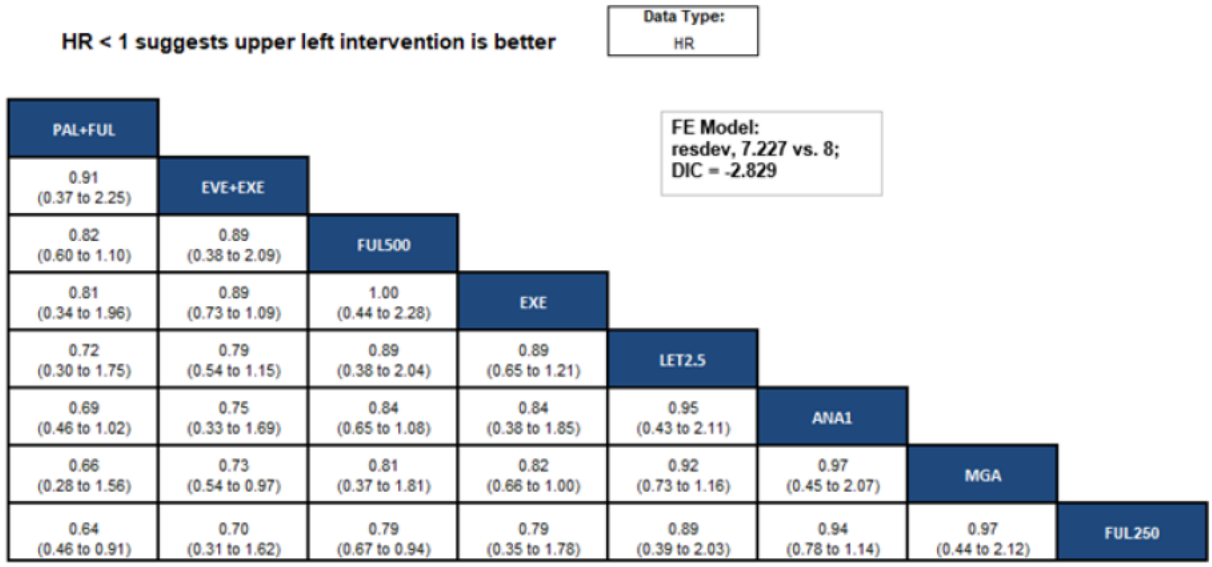
A fixed effect model was chosen over a random effects model because the network structure was largely comprised of single study connections which limit the ability of a random effects model to estimate between-study variance, resulting in wide credible intervals.

Source: [ITC submitted by Pfizer (04.03_Ibrance_Appendix A mBC progressed after prior endocrine therapy NMA.docx), Figure 1.1][10]

Overall survival

Results for the fixed effect NMA for OS (Figure 7.4) showed that palbociclib + fulvestrant was associated with an improved OS compared to all other comparators, although results were not significant for most comparisons. Secondary measures of treatment effect found that the palbociclib + fulvestrant combination had the highest probability of being the best treatment, the highest SUCRA, and the best average rank for OS.

Figure 7.3: Pairwise comparisons from the fixed effect NMA, OS (reported as HRs with 95% CrIs)



Pairwise comparisons from the fixed effect model are shown in terms of summary HRs and 95% CrIs. Each value reflects a comparison between treatments belonging to the intersecting column and row, with additional benefit indicated for the treatment in the column. Model fit statistics are also presented.
A fixed effect model was chosen over a random effects model because the network structure was largely comprised of single study connections which limits the ability of a random effects model to estimate between study variance, resulting in wide credible intervals.
Abbreviations: ANA = anastrozole; CrI = credibile interval; DIC = deviance information criterion; EVE = everolimus; EXE = exemestane; FE = fixed effect; FUL = fulvestrant; HR = hazard ratio; LET = letrozole; MGA = megestrol acetate; NMA = network meta-analysis; OS = overall survival; PAL = palbociclib.

Source: [ITC submitted by Pfizer (04.03_Ibrance_Appendix A mBC progressed after prior endocrine therapy NMA.docx), Figure 1.1][10]

7.1.4 Summary

The quality of the ITC provided by the submitter[10] was assessed according to the recommendations made by the ISPOR Task Force on Indirect Treatment Comparisons.[77] Details of the critical appraisal are presented in Table 7.2.

Table 7.2: Adapted ISPOR questionnaire to assess the credibility of an indirect treatment comparison or network meta-analysis†

ISPOR Questions	Details and Comments
1. Is the population relevant?	**Yes.** The study population for the submitted ITC matched the review indication, which was to evaluate the efficacy and safety of palbociclib + fulvestrant in patients with HR+/HER2- locally ABC or mBC after progression on endocrine therapy. Across the 11 studies included in NMA, the majority of patients

Table 7.2: Adapted ISPOR questionnaire to assess the credibility of an indirect treatment comparison or network meta-analysis†

ISPOR Questions	Details and Comments
	(47% to 100%) enrolled in the 11 RCTs, included for NMA, had a confirmed HR+ status but HER2 status was only reported in two studies. The proportion of patients receiving prior endocrine therapy in the advanced setting varied widely across studies from 10.2% to 89.2%
2. Are any critical interventions missing?	**No.** Although chemotherapies were not included as comparators in the submitted ITC, the Clinical Guidance Panel (CGP) agreed that appropriate comparators should be current, accepted norms for hormonal treatment of HR+/HER2- locally ABC or mBC in Canada, noting that in practice the majority of potentially eligible patients are post-menopausal women in whom chemotherapy would not be a very relevant therapy.
3. Are any relevant outcomes missing?	**Yes, in part.** The following outcomes were assessed: OS and PFS/TTP. Other relevant outcomes such as ORR, quality of life, and safety results were excluded from the submitted NMA.
4. Is the context (e.g., settings and circumstances) applicable to your population?	**Yes.** The settings of the included trials were similar, and applicable to the Canadian population.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes.** The submitter conducted a systematic review to identify eligible studies for the ITC. Details of the systematic literature review process was provided in the submitter's ITC report as well as the journal article published by Wilson et al.[35]
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**No.** There were no closed loops in the ITC.
7. Is it apparent that poor quality studies were included thereby leading to bias?	**No.** A risk of bias assessment was conducted for the included studies by the submitter, using the National Institute for Health and Care Excellence (NICE) single technology appraisal checklist; and the results of this assessment was included in the ITC report as an appendix.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**Unclear.** It is unclear if there was selective reporting of outcomes in the included trials.
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?	**No.** According to the submitted ITC report, heterogeneity was assessed by summarizing study and patient characteristics across the included studies, and by conducting sensitivity analyses where possible. Results from the sensitivity analyses for PFS/TTP and OS, which were provided in the submitted ITC, were consistent with those derived in the reference case analysis.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Not applicable**

Table 7.2: Adapted ISPOR questionnaire to assess the credibility of an indirect treatment comparison or network meta-analysis†	
ISPOR Questions	**Details and Comments**
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Yes. a Bayesian NMA and pairwise meta-analyses were conducted, using the methods outlined by the NICE to pool trial results
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	**Not applicable.** There was no closed loop.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Not applicable.** There was no closed loop.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**Yes, in part.** To reduce the risk of heterogeneity/inconsistency, the analysis was performed at the drug level (versus class level) and was stratified by individual doses of the various treatments of interest. Following pCODR's request for additional information, the submitter provided evidence that the proportionality assumption was not violated for the analyses of time-to-event data in the PLAOMA-3 trial (i.e., there was no time-effect interaction). However, it is not clear if the proportional hazards assumption held within all trials in the network.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes.** Both fixed effect and random effects models were conducted. It was noted in the submitter's report that the ability of the analysis to reliably estimate between-study variance was limited due to the large number of single-study connections in the network. Therefore, the submitter focused their report on findings from the fixed effect model but the results of the random effects model was also provided in an appendix.
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.** To reduce heterogeneity, sensitivity analyses were conducted where possible. According to the submitter's report meta-regression analyses or subgroup/sensitivity analyses related to certain characteristics of interest (not specified) was not possible due to the presence of several single study connections between interventions.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes.** The networks are presented in Figure 7.1 and Figure 7.2.
19. Are the individual study results reported?	**Yes.** The submitter provided the baseline characteristics of the trials and the HRs of the outcomes (PFS/TTP and OS) used in the NMA.

Table 7.2: Adapted ISPOR questionnaire to assess the credibility of an indirect treatment comparison or network meta-analysis†

ISPOR Questions	Details and Comments
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	No. no closed loops were included in the NMA.
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% credible intervals) were provided, where applicable.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes. The interventions were ranked using league tables and the Surface Under the Cumulative RAnking curve (SUCRA) method.
23. Is the impact of important patient characteristics on treatment effects reported?	No.
24. Are the conclusions fair and balanced?	Yes. The results of the NMA showed that, in terms of PFS/TTP, palbociclib + fulvestrant was statistically superior to all endocrine monotherapies included in the network, except everolimus + exemestane for which no difference was found. For OS, point estimates of effect resulting from the ITC suggested an OS benefit for palbociclib + fulvestrant when compared with other comparators (HRs < 1). However, the overlapping CrIs suggested that there were not statistically significant differences between palbociclib + fulvestrant and all other comparators.
25. Were there any potential conflicts of interest?	Not reported.
26. If yes, were steps taken to address these?	Not reported.

HR = hazard ratio; ISPOR = International Society For Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparisons; NICE = the National Institute for Health and Care Excellence (United Kingdom); NMA = network meta-analysis; PFS = progression-free survival; TTP = time to progression

† Adapted from Jansen, Value Health. 2014;17(2):157-73[77]

Conclusions:

Results of the submitted NMA showed that palbociclib + fulvestrant was associated with a superior PFS/TTP compared with endocrine monotherapies, and no difference compared with everolimus + exemestane for the treatment of HR+/HER2- locally ABC or mBC patients who progressed after prior endocrine therapy. A trend towards improvement in OS was observed when the palbociclib + fulvestrant combination was indirectly compared with other endocrine therapies. However, OS differences were not statistically significant based on the overlapping CrIs.

Although alignment of these findings with direct evidence lends credibility to the analysis, these results should be interpreted with attention due to the limitations that arise from the lack of closed loops in the network, large number of single-study connections in the network, and lack of indirect comparisons for safety data, other efficacy outcomes (objective response rate, etc.), and patient-reported outcomes. From a technical perspective, the NMA methodology is relatively sound, but this does not necessarily eliminate the uncertainty in the data outlined above.

8 COMPARISON WITH OTHER LITERATURE

The Methods Team did not identify any relevant information that would be important for the 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 palbociclib (Ibrance) plus fulvestrant (Faslodex) for 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 palbociclib (Ibrance) plus fulvestrant (Faslodex) for metastatic breast cancer. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials September 2018, Embase 1974 to 2018 October 09, Ovid MEDLINE(R) ALL 1946 to October 09, 2018
Search Strategy:

#	Searches	Results
1	(Ibrance* or Palbociclib* or "PD 0332991" or PD0332991 or PD 332991 or PD332991 or "PF 00080665" or PF00080665 or G9ZF61LE7G).ti,ab,ot,kf,kw,hw,rn,nm.	2846
2	exp Breast Neoplasms/	750969
3	(((breast* or mamma or mammar* or lobular*) and (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or metasta* or neoplas* or sarcoma* or tumo?r* or mass*)) or mBC or m-BC or LABC).ti,ab,kf,kw.	873765
4	or/2-3	1010940
5	1 and 4	1666
6	5 use medall	344
7	5 use cctr	176
8	*palbociclib/	546
9	(Ibrance* or Palbociclib* or "PD 0332991" or PD0332991 or PD 332991 or PD332991 or "pf 00080665" or pf00080665).ti,ab,kw,dq.	1991
10	or/8-9	2020
11	exp Breast Tumor/	750969
12	(((breast* or mamma or mammar* or lobular*) and (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or metasta* or neoplas* or sarcoma* or tumo?r* or mass*)) or mBC or m-BC or LABC).ti,ab,kw,dq.	873403
13	or/11-12	1011582
14	10 and 13	1249
15	14 use oemezd	766
16	15 and conference abstract.pt.	417
17	limit 16 to yr=2013-current	402
18	15 not conference abstract.pt.	349
19	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1104652
20	Randomized Controlled Trial/	985066
21	exp Randomized Controlled Trials as Topic/	278225
22	"Randomized Controlled Trial (topic)"/	149670
23	Controlled Clinical Trial/	550740
24	exp Controlled Clinical Trials as Topic/	289403
25	"Controlled Clinical Trial (topic)"/	9581
26	Randomization/	175608
27	Random Allocation/	192433
28	Double-Blind Method/	394912
29	Double Blind Procedure/	153517

30	Double-Blind Studies/	258810
31	Single-Blind Method/	74766
32	Single Blind Procedure/	32535
33	Single-Blind Studies/	76713
34	Placebos/	324967
35	Placebo/	323975
36	Control Groups/	111316
37	Control Group/	111224
38	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3948932
39	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	772626
40	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2929
41	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	2574034
42	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	93576
43	allocated.ti,ab,hw.	174621
44	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	112734
45	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	24377
46	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	924
47	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	10827
48	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	17027
49	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	125340
50	or/19-49	5653498
51	17 and 50	149
52	6 or 18	693
53	50 and 52	208
54	7 or 53	384
55	remove duplicates from 54	300
56	51 or 55	449
57	limit 56 to english	415

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

Search	Query	Items found
#10	Search (#8 AND publisher[sb]) Filters: English	20
#9	Search (#8 AND publisher[sb])	20
#8	Search (#3 AND #7)	341
#7	Search (#4 OR #5 OR #6)	400369
#6	Search (mBC[tiab] OR m-BC[tiab] OR LABC[tiab])	6607

#5	Search **((breast*[tiab] OR mamma[tiab] OR mammar*[tiab] OR lobular*[tiab]) AND (cancer*[tiab] OR carcinoid*[tiab] OR carcinoma*[tiab] OR carcinogen*[tiab] OR adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab] OR malignan*[tiab] OR metasta*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumorous[tiab] OR tumour*[tiab] OR mass[tiab] OR masses[tiab]))**	352076
#4	Search **"Breast Neoplasms"[Mesh]**	267888
#3	Search **(#1 OR #2)**	582
#2	Search **(Ibrance*[tiab] OR Palbociclib*[tiab] OR PD 0332991[tiab] OR PD0332991[tiab] OR PD 332991[tiab] OR PD332991[tiab] OR G9ZF61LE7G[rn])**	582
#1	Search **"palbociclib" [Supplementary Concept]**	276

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

4. Grey Literature search via:

   Clinical Trial Registries:

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

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

   Search: Ibrance/palbociclib, 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: Ibrance/palbociclib, Breast Cancer

   Conference abstracts:

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

   San Antonio Breast Cancer Symposium (SAVCS)
   https://www.sabcs.org/

   Search: Ibrance/palbociclib, Breast Cancer – last 5 years

Literature Search Methods

Detailed Methododolgy

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-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (September 2018) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Ibrance, palbociclib, and breast cancer.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. 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 Febuary 06, 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 San Antonio Breast Cancer Symposium (SAVCS) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One 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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