CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Palbociclib (Ibrance) for Advanced Breast Cancer - Resubmission

November 21, 2016

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INQUIRIES

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

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

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

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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 for advanced breast cancer resubmission. 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 for advanced 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 for advanced breast cancer, a summary of submitted Provincial Advisory Group Input on palbociclib for advanced breast cancer, and a summary of submitted Registered Clinician Input on palbociclib for advanced 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 letrozole compared with standard endocrine therapy alone as first-line treatment in post-menopausal women with estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer (ABC).

Health Canada has issued marketing authorization with conditions for use of palbociclib in combination with letrozole for the treatment of post-menopausal women with ER+, HER2- ABC as initial endocrine-based therapy for their metastatic disease. The market authorization is conditional upon results from PALOMA-2 confirmatory trial, which are now available and the basis of this resubmission.

The recommended dose of palbociclib is 125 mg orally once daily for 21 consecutive days followed by 7 days off treatment. Palbociclib should be taken in combination with letrozole 2.5 mg once daily continuously. Treatment should continue as long as patients are deriving clinical benefit from therapy.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Two randomized controlled trials (RCTs), PALOMA-2[1,2] and PALOMA-1,[3] were identified that met the eligibility criteria of this review. At the time this report was completed the PALOMA-1 trial was published and the PALOMA-2 trial was only available in abstract form; therefore, the majority of PALOMA-2 data summarized in this report comes directly from documents provided by the Submitter.[2]

Trials

The PALOMA trials were both international, multi-centred randomized trials. PALOMA-1, which preceded PALOMA-2, was a phase 2 trial evaluating the initial efficacy and safety of palbociclib-letrozole compared to letrozole alone as first-line treatment in women with ER+, HER2- ABC. PALOMA-2, a placebo-controlled phase 3 trial, was designed to confirm the results of PALOMA-1 and determine whether palbociclib-letrozole was indeed superior to letrozole alone, in terms of prolonging progression-free survival (PFS), among post-menopausal women with ABC. The trials, both funded by Pfizer, compared identical active interventions and schedules, assessed similar outcomes, and enrolled patients based on very similar eligibility criteria that included the following:

- ≥18 years of age
- Locally recurrent or metastatic disease not amenable to surgery
- No prior treatment for ABC, including any previous treatment with a CDK inhibitor
- Specifically excluded patients with active brain metastases

Aside from trial phase, the main features that distinguished the trials included the following:

- PALOMA-2:
    - Included patients with an ECOG performance status of 0 to 2
    - Excluded patients who had disease recurrence while on or within 12 months of completing (neo)adjuvant treatment with letrozole or anastrozole
    - Included a placebo-control and double-blinding
    - Stratified randomization by prior hormone therapy, in addition to disease-site and disease-free interval
    - Assessed patient-reported quality of life (QOL) using validated instruments [Breast Functional Assessment of Cancer Therapy (FACT-B) and EuroIQoL five dimensions (EQ-5D)]

- PALOMA-1:
    - Included patients with a ECOG performance status of 0 or 1
    - Excluded patients receiving letrozole as (neo)adjuvant treatment within 12 months of study entry
    - Open-label design
    - Assessed patient-reported pain severity and interference using the modified Brief Pain Inventory short-form (BPI-sf)
    - Multiple data-driven trial protocol changes compromised the statistical analysis plan (SAP) of the trial raising concern about the internal validity of the trial and the magnitude of the treatment effect observed

PALOMA-2 enrolled patients between February 2013 and July 2014 at 186 sites from 17 countries, including Canada (14 sites). Patients were randomized to treatment with either palbociclib-letrozole or placebo-letrozole. Randomization was stratified by disease site (visceral vs. non-visceral), disease-free interval from the end of (neo)adjuvant treatment to disease recurrence (≤12 months, >12 months, versus de novo metastatic disease), and prior hormonal therapy (yes/no). The primary outcome of the trial was investigator-assessed PFS. The secondary outcomes included overall survival (OS), objective response rate (ORR), duration of response, disease control (defined as complete plus partial response plus stable disease ≥24 weeks) and QOL. All efficacy analyses were based on intent-to-treat (ITT) and a blinded independent central review (BICR) was prospectively planned but conducted retrospectively to verify tumour response and disease progression

outcomes. Sponsor data analysts were blinded to treatment assignment during interim efficacy analyses but were unblinded to final efficacy analyses.

PALOMA-1 enrolled patients between December 2009 and May 2012 from 50 sites in 12 countries including Canada. Enrolment was conducted using a sequential cohort design. In Cohort 1, patients were enrolled based on ER+ and HER2- status alone (biomarker-unselected group), whereas in Cohort 2 patients were also required to have amplification of cyclin D1 (CCND1) and/or loss of p16 (biomarker-selected group). Randomization was stratified by disease site (i.e., visceral, bone only, or other) and disease-free interval (>12 months from the end of adjuvant treatment to recurrence vs. ≤12 months from the end of adjuvant treatment to recurrence or de novo metastatic disease). The primary outcome was investigator assessed PFS. The secondary outcomes included OS, ORR, clinical benefit (defined the same as disease control), duration of response, patient-reported pain, and safety.

The PALOMA-1 trial protocol was amended eight times over the course of the trial, and three amendments involved major changes to the SAP, which occurred after examinations of the trial data. For a more detailed explanation of SAP changes refer to section 6.3.2.1. The final analysis of PFS was conducted according to ITT. Due to the number of data-driven amendment changes, and also considering the open-label design and small sample size of the trial, the FDA requested the Sponsor conduct a BICR of the PFS data.[4] The BICR was carried out retrospectively and considered a secondary outcome of the trial.

Populations

In general, the distributions of patient characteristics appeared similar in the PALOMA trials, with the exception of higher proportions of patients with non-visceral site of disease and prior receipt of hormonal therapy in PALOMA-2; and more patients in PALOMA-1 with a shorter disease-free interval (≤ 12 months) from completion of (neo)adjuvant therapy to recurrence.

Of the 666 patients randomized in PALOMA-2, 444 patients were randomized to the palbociclib-letrozole treatment group and 222 were allocated to placebo-letrozole. The median age of patients was 62 years, with approximately 39% of patients aged 65 or older. Most patients were white (77%), from European countries (46%), and had an ECOG performance status of 0 (54%). Canadian patients comprised approximately 11% (n=70) of the trial population. A majority of patients had stage IV disease (97%) and approximately a third of patients presented with de novo stage IV disease (3%). Site of disease was generally equally distributed for visceral (49%) and non-visceral spread (51%). Disease-free interval was ≤ 12 months in 22% of patients and >12 months in 41% of patients. More patients received hormonal therapy (56%) as (neo)adjuvant treatment for their primary diagnosis than chemotherapy (48%), with tamoxifen being the most commonly received hormonal therapy (46%).

In PALOMA-1 (Combined Cohort), a total of 165 patients were randomly assigned; 84 were randomized to palbociclib-letrozole and 81 to letrozole alone. The median age of patients was 63 years, with almost all patients presenting with stage IV disease (98%). The majority of patients were white (90%)[5] and had an ECOG status of 0 (55%). Canadian patients comprised 3% (n=5) of the trial population. Site of disease was categorized as visceral, bone only, or other in 48%, 18%, and 34% of patients, respectively. A large proportion of patients had not received any prior systemic therapy, with 49% of patients presenting with de novo advanced disease. Among patients previously treated in the adjuvant setting, 43% had received chemotherapy and 33% had received hormone therapy. Of the patients treated with hormone therapy, 29% were treated with tamoxifen and 17% were treated with aromatase inhibitors (AIs). More patients in the palbociclib-letrozole group had a

shorter disease-free interval (≤ 12 months) from completion of adjuvant therapy to recurrence compared to the letrozole group; however, the increased percentage of patients with de novo disease in the combined treatment arm likely accounts for some of this difference.

Interventions

In both PALOMA trials, all patients received a continuous regimen of letrozole at a dose of 2.5 mg once daily. Patients allocated to the experimental treatment groups of each trial received palbociclib at a dose of 125 mg once a day for three weeks followed by one week off in a 28-day cycle. In PALOMA-2, placebo was administered once daily on the same schedule as palbociclib. Treatment was continued until disease progression, unacceptable toxicity, withdrawal of consent, or death. Dose modifications were permitted in both trials. In PALOMA-2, no dose reductions of letrozole were allowed; however, patients experiencing specific adverse events could have their dose interrupted or delayed. Crossover was not permitted in either trial.

In PALOMA-2, the median duration of treatment was 603 days for palbociclib and 617 days for letrozole. The median relative dose intensity for palbociclib and letrozole was 93% (116.25 mg/day) and 100% (2.5 mg/day), respectively. In the placebo-letrozole group, the median duration of treatment was 413 days for placebo and 420 days for letrozole, and the median relative dose intensity was 100% for both study drugs. In PALOMA-1, the median duration of treatment for patients receiving palbociclib was 420 days. The relative dose intensity in the palbociclib-letrozole group was 94% (117.5 mg/day). Dose reductions, interruptions and cycle delays all occurred more frequently in the palbociclib-letrozole treatment group of each trial.

At the date of final data analysis in each trial, the majority of patients had discontinued treatment. Considering all treatment groups in both trials, the primary reason for discontinuation was disease progression. Both PALOMA-2 and PALOMA-1 encountered a substantially large number of protocol deviations. For a more detailed explanation of the specific deviations that occurred in each trial refer to section 6.3.2.1.

Outcomes

The key efficacy data from the PALOMA trials are summarized in Table 1. In both trials, PFS by investigator assessment was significantly prolonged in patients treated with palbociclib-letrozole compared to letrozole alone, after approximately two years of follow-up. The PFS benefit associated with palbociclib-letrozole was in the range of 10 months (over letrozole alone) in each trial, and was consistently demonstrated in almost all patient subgroups examined. The results of BICR analyses of PFS, conducted in both trials, confirmed the median PFS benefit but estimated the magnitude of overall benefit to be lower than the investigator assessment.

All secondary outcomes examined in each trial, including ORR, duration of response, and disease control/clinical benefit, also favoured palbociclib-letrozole (Table 1). Overall survival data were immature at the time of the final analysis of PFS data in both trials; therefore, final results are not yet available for this outcome. The addition of palbociclib to letrozole did not appear to affect health-related QOL or pain outcomes as measured by FACT-B, EQ-5D, and modified BPI-sf instruments, although these analyses have limitations that are detailed in section 6.3.2.1.

Considering both PALOMA trials, palbociclib-letrozole combined treatment was associated with a greater frequency of all grade and grade 3-4 adverse events (AEs) compared to letrozole, with grade 3-4 neutropenia being the most frequently reported AE (range, 54%-66%, versus 4%-13% with letrozole). Infections, leucopenia and fatigue were also more

common with combined treatment. In both trials, compared to letrozole, treatment interruptions, dose/cycle delays and permanent treatment discontinuation due to AEs were also more prevalent in patients receiving palbociclib-letrozole.

Limitations

The limitations associated with the PALOMA trials are fully discussed in section 6.3.2.1.

The quality of the PALOMA-2 trial was challenging to appraise in the absence of a peer-reviewed trial publication. The appraisal was based on a single abstract and data provided by the Submitter, which are sources of evidence that fall short of providing a comprehensive account of all aspects of trial conduct. Therefore, additional limitations may come to light upon full publication of the trial. Overall, the trial was well conducted owing to specific design features (e.g., placebo control, double-blind method). These features address some of the design shortcomings of the PALOMA-1 trial (described below). However, limitations were noted, which included the following:

- The very large number of major protocol deviations that occurred during the trial is a concern. The impact of the most prevalent deviations (i.e., prohibited concomitant medications, investigational product/treatment) on the results obtained should have been assessed in sensitivity analyses to fully assess their influence on the trial results.
- The assessment of QOL should be interpreted with caution as the number of patients who contributed to assessments substantially declined over the course of the trial, which raises uncertainty about the reliability of the QOL findings.
- Selective reporting is a limitation to the PALOMA-2 data presented in this report as the trial has yet to be published in the public domain and undergo peer-review.

The PALOMA-1 trial suffered from multiple flaws in design and execution. Many of the issues associated with the trial relate to the fact that it was not designed to be a registration trial for regulatory approval. This partially explains why more rigorous methods of trial conduct (e.g., prospectively planned BICR of outcome data and data analysis) were not done and why the sample size is too small to reliably determine the true effect size associated with palbociclib-letrozole. The multiple data-driven amendment changes compromised the SAP of the trial and cast doubt on the integrity of the obtained results and the magnitude of the reported treatment effect estimates.

Table 1: Key efficacy outcomes in the PALOMA-1 and PALOMA-2 trials.

Trials	PALOMA-2[1,2]		PALOMA-1[3]	
Treatment Groups	Palbociclib + Letrozole	Placebo + Letrozole	Palbociclib + Letrozole	Letrozole
Median follow-up, months	23.0	22.3	29.6	27.9
Patients remaining on treatment, n (%)	199 (45)	61 (28)	19 (23)	8 (10)
Primary Outcome - Investigator Assessed PFS[A]	n=444	n=222	n=84	n=81
No. PFS events (%)	194 (43.7)	137 (61.7)	41(48.8)	59 (72.8)
Median PFS, months (95% CI)	24.8 (22.1 to NE)	14.5 (12.9 to 17.1)	20.2 (13.8 to 27.5)	10.2 (5.7 to 12.6)
Hazard ratio (95% CI; one-sided p-value)	0.58 (0.46 to 0.72; p<0-000001)		0.49 (0.32 to 0.75; p=0.0004)	
Secondary Outcome - BICR-assessed PFS[A,H]	n=444	n=222	n=84	n=81
No. PFS events (%)	152 (34.2)	96 (43.2)	31(36.9)	33 (40.7)
Median PFS, months (95% CI)	30.5 (27.4 to NE)	19.3 (16.4 to 30.6)	25.7 (17.7 to NR)	14.8 (9.3 to 20.4)
Hazard ratio (95% CI; one-sided p-value)	0.65 (0.51 to 0.84; p=0.0005)		0.62 (0.38 to 1.02; p=0.03)	
Other Key Secondary Outcomes	n=444	n=222	n=84	n=81
Objective Response Rate[B] % (95% CI)	42.1 (37.5 to 46.9)	34.7[C] (28.4 to 41.3)	43 (32 to 54)	33 (23 to 45)
One-sided p-value	p=0.03		p=0.13	
Duration of Response[D]				
Median duration in months (95% CI)	22.5 (19.8 to 28)	16.8 (15.4 to 28.5)[C]	20.3 (13.4 to 25.8)	11.1 (9.3 to 31.6)
One-sided p-value	p=NR		p=NR	
Clinical Benefit[E]				
No. (%) patients achieving clinical benefit	NR (84.9)	NR (70.3)	68 (81)	47 (58)
One-sided p-value	p<0.0001		p=0.0009	
Overall Survival				
No. deaths	95	38	30	31
Median, months (95% CI)	NA	NA	37.5 (28.4 to NE)	33.3 (26.4 to NE)
Hazard ratio (95% CI; two-sided p-value)	NA	NA	0.81 (0.49 to 1.35; p=0.42)	
Patient-reported Outcomes	n=439	n=218	n=76	n=74
FACT-B Total Score,[F] mean change from baseline (95% CI)	-0.106 (-1.42 to 1.21)	1.196 (-0.32 to 2.71)	NA	NA
Mean Difference (95% CI), p-value	-0.325 (-2.63 to 1.98; p=0.7822)		NA	NA
EQ-5D,[G] mean change from baseline	0.014 (0.00 to 0.03)	-0.010 (-0.03 to 0.01)	NA	NA
Mean Difference (95% CI), p-value	0.023 (-0.004 to 0.051; p=0.0925)		NA	NA
Pain Severity Scale,[H] mean change from baseline (SE) [I,J]	NA	NA	0.4 (0.29)	0.2 (0.32)
Mean Difference (95% CI), p-value	NA	NA	0.2 (-0.7 to 1.0; p=0.69)	
Pain Interference Scale, mean change from baseline (SE)	NA	NA	0.8 (0.34)	0.4 (0.30)
Mean Difference (95% CI), p-value	NA	NA	0.4 (-0.5 to 1.3), p=0.33	

Harms Outcomes			n=83	n=77
Any grade adverse event, n (%)	439 (99)	212 (96)	82 (99)	65 (84)
Grade 3-4 adverse event, n (%)	336 (76)	54 (24)	63 (76)	16 (21)
Any serious adverse event, n (%)	87 (20)	28 (13)	7 (8)	5 (6)
Adverse event leading to treatment discontinuation, n (%)	43 (10)	13 (6)	11 (13)[K]	2 (3)[L]

Abbreviations: **BICR** - blinded independent central review; **CI** - confidence interval; **EQ-5D** - EuroQol 5-Dimensions; **FACT-B** - Functional Assessment of Cancer Therapy Breast Specific Module; **ITT** - intent-to-treat; **NA** - not available/applicable; **No./n** = number; **NE** - not estimable; **NR** - not reached; **PFS** - progression-free survival.

Notes:
[A] Defined at the time from randomization to disease progression or death on study.
[B] Defined as the sum of complete plus partial responses.
[C] Includes one patient with bone only disease at baseline; all other patients had measurable disease at baseline.
[D] Duration of complete or partial response.
[E] Defined as the sum of complete plus partial responses and stable disease for 24 weeks or more.
[F] FACT-B total score is the sum of FACT-G subscales (physical well-being, social/family well-being, emotional well-being, functional well-being) and breast cancer subscale; based on patients who completed >80% of questions and have valid scores for subscales.
[G] EQ-5D based on patients who completed all five items needed to calculate index-based summary score at respective cycle.
[H] As measured by the Modified Brief Pain Inventory-Short Form Pain Severity and Pain Interference Scales.
[I] Source: FDA Medical Review and Evaluation Report[5]
[J] Source: ClinicalTrials.gov clinical trial record[6]
[K] Of these patients, six (7%) discontinued due to a treatment-related adverse event.
[L] The two patients (2%) discontinued due to a treatment-related adverse event.

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

Two patient advocacy groups, Rethink Breast Cancer (Rethink) and Canadian Breast Cancer Network (CBCN), provided input. Both Rethink and CBCN reported that current treatment options and effectiveness vary among type of cancer, location of cancer, and how symptoms are experienced. From a patient's perspective, managing a diagnosis of metastatic breast cancer is challenging, as current treatment options for metastatic breast cancer are only effective at prolonging progression-free disease, and most cases of advanced disease will progress and symptoms will worsen. According to Rethink and CBCN, patients' expectations for the new treatment under review are the following: (1) to delay the progression of the disease, (2) to relieve cancer-related symptoms, and (3) to improve on quality of life.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Generalizability of PALOMA-2 trial to palbociclib in combination with other aromatase inhibitors
- Data on use in patients who have failed other aromatase inhibitors

- Monthly monitoring and bloodwork for neutropenia, which is not required with letrozole monotherapy

Economic factors:

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

Registered Clinician Input

Two registered clinicians provided input. Clinician input identified that palbociclib plus letrozole have added benefits over letrozole monotherapy. However, it was noted that no overall survival benefit was achieved with PALOMA-1 and is not yet available for PALOMA-2. In addition, there are added toxicities of palbociclib not seen with letrozole monotherapy.

Summary of Supplemental Questions

A manufacturer-submitted network meta-analysis (NMA), comparing palbociclib-letrozole to other endocrine therapies as first-line treatment in post-menopausal women with ER+, HER2- ABC, was summarized and critically appraised using the ISPOR Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire. The primary NMA found a statistically significant difference in PFS/TTP in favour of palbociclib-letrozole relative to letrozole, anastrozole, exemestane and tamoxifen. All sensitivity analyses performed indicated the PFS results were robust to differences in the patient and study characteristics assessed. No differences in OS were demonstrated. An expanded network sensitivity analysis, which was performed post-hoc and included other combination therapies, showed superior PFS/TTP with palbociclib-letrozole compared to anastrozole, tamoxifen, letrozole, exemestane, fulvestrant 250mg, and anastrozole-fulvestrant, while no differences were observed between palbociclib-letrozole and everolimus-exemestane or high-dose fulvestrant (500mg). No differences in OS were observed between any of the regimens examined. The quality assessment judged the overall relevance and credibility of the NMA to be insufficient. The main limitations of the NMA include omission of other combination therapies from the primary NMA (versus only single-agent regimens), failure to include other important outcomes (i.e., adverse events), significant heterogeneity across included trials, and the inability to adjust for the influence of heterogeneity due to constraints in the structure of the evidence networks (e.g., single trial connections or small numbers of trials). The conclusions drawn from the NMA should be interpreted with caution.

See section 7.1 for more information.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

Table 2.2 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 combined with letrozole in women with ER-positive, HER2-negative advanced/metastatic breast cancer (treatment naïve).

Domain	Factor	Evidence and PAG input	Generalizability Question	CGP Assessment of Generalizability
Population	ECOG PS	**PALOMA-1:** patients with ECOG PS of 2 or greater were excluded. Combined cohort: ECOG 0: n=91/165 (55%) ECOG 1: n= 74/165 (45%) **PALOMA-2:** patients with ECOG PS of 3 or greater were excluded. ECOG 0: n=359/666 (54%) ECOG 1: n= 295/666 (44%) ECOG 2: n=12/666 (2%)	Do the trial results apply to patients with an ECOG PS of 2 or greater? If so, why?	Most patients in clinical practice will have an ECOG PS of 0 or 1. As benefit for patients with ECOG 2 cannot be concluded from the very small number of patients with ECOG 2 in the trial, the combination should be limited to patients with ECOG 0 or 1.
	Disease stage	**PALOMA-1:** most patients in the trial had stage IV disease (versus stage III). Combined cohort: Stage III: n=3/165 (2%) Stage IV: n=162/165 (98%) **PALOMA-2:** Stage III: n=17/666 (3%) Stage IV: n=649/666 (97%)	Is this representative of how patients present in Canadian practice? Does this limit the interpretation of the trial results to stage IV patients?	Although the majority of the patients had Stage IV disease, the CGP feels that it is reasonable to include unresectable locally advanced breast cancer patients.
	Brain metastases	**PALOMA-1:** patients with brain metastases were excluded. **PALOMA-2:** patients with active uncontrolled or symptomatic CNS metastases, carcinomeningitis or leptomeningeal disease were excluded.	Do the trial results apply to patients with active brain metastases? If so, why?	There is no evidence to support the use of the combination in patients with active brain metastases; these patients have a particularly poor prognosis.

Domain	Factor	Evidence and PAG input	Generalizability Question	CGP Assessment of Generalizability
	Time since progression (disease-free interval)	**PALOMA-1:** a statistically significant treatment effect in PFS was observed in favour of the palbociclib-letrozole group in all patient subgroups with the exception of patients in the ≤ 12 months since adjuvant treatment to recurrence (excluding de novo presentation) category. This was the smallest subgroup examined (n=29; HR=0.77, 95% CI, 0.23-2.5).[A] **PALOMA-2:** a statistically significant treatment effect in PFS was observed in favour of palbociclib-letrozole in all disease-free interval patient subgroups: • ≤ 12 months from (neo) adjuvant treatment to recurrence (n=147, HR=0.50, 95% CI, 0.33-0.76) • >12 months from (neo) adjuvant treatment to recurrence (n=271, HR=0.52, 95% CI, 0.37-0.73) • De novo metastases (n=248, HR=0.67, 95% CI, 0.46-0.99)	Are the results of this subgroup likely valid? If so, does this finding limit the interpretation of the trial results to patients with a disease interval >12 months?	Benefits were seen in all subgroups. The de novo population in PALOMA-2 had the least benefit of 33% compared to 50% and 48% in ≤12 months and >12 months from adjuvant treatment, respectively, indicating that a benefit is seen regardless of when metastatic disease presents, and that the addition of palbociclib to letrozole improves PFS.
	De novo disease	**PALOMA-1:** 49% (n=81) of patients presented with de novo advanced/metastatic disease (had not received any prior systemic therapy). **PALOMA-2:** 37% (n=248) of patients presented with de novo advanced/metastatic disease (had not received any prior systemic therapy).	Do the trial results apply to patients with de novo disease? If so, why?	This does not represent the typical population of women with advanced/metastatic breast cancer in Canada. Theoretically, the fact that patients had received no prior chemotherapy could have enhanced the benefit seen with targeted therapy. However, the CGP are unable to comment further. The benefit seen was marginal, with borderline significance, indicating that the largest benefit with palbociclib-letrozole is with prior adjuvant endocrine therapy, which is typical of the Canadian population with ER+/HER2- ABC.
Comparator	Standard of care:	PAG noted that various AIs are available for initial	Are the findings of this trial limited to	Although the CGP were of the opinion that the three

Domain	Factor	Evidence and PAG input	Generalizability Question	CGP Assessment of Generalizability
	other endocrine therapy	treatment in ER+/HER2- disease, including anastrozole, exemestane and letrozole. Both PALOMA 1 and 2 compared palbociclib-letrozole to letrozole alone. A submitted NMA found a statistically significant difference in PFS/TTP in favour of palbociclib-letrozole relative to letrozole, anastrozole, exemestane, and tamoxifen. No differences in OS were demonstrated. An expanded NMA sensitivity analysis, (performed post-hoc to include other combination therapies) showed superior PFS/TTP with palbociclib-letrozole relative to anastrozole, tamoxifen, letrozole, exemestane, fulvestrant 250mg, and anastrozole-fulvestrant, but no difference between palbociclib-letrozole and everolimus-exemestane or high-dose fulvestrant 500mg. The quality assessment performed judged the overall relevance and credibility of the NMA to be insufficient. The main limitations include omission of other combination therapies from the primary NMA as well as other outcomes (adverse events), and significant heterogeneity across included trials. The conclusions drawn from the NMA should be interpreted with caution.	letrozole, or are they generalizable to other AIs? Why or why not?	available AIs have similar activity, direct comparisons and toxicity data for other combinations are lacking. Data are only available in second-line with fulvestrant. The CGP felt the combination of palbociclib with an AI should be limited to letrozole based on the current evidence. The CGP were also unable to conclude the combination of palbociclib-letrozole compared to other endocrine therapies was better given exclusion of relevant studies from the primary NMA, significant heterogeneity across the included trials, and the inability to adjust for the influence of heterogeneity due to constraints in the structure of the evidence networks. However, it is the opinion of the CGP that it is likely that a combination therapy is better than single agent therapy.

Domain	Factor	Evidence and PAG input	Generalizability Question	CGP Assessment of Generalizability
Outcomes	Short-term survival data	**PALOMA-1:** OS data were deemed immature at the time of data analysis. Median follow-up time was approximately 30 months; at this time point, the number of deaths was 30 and 31 in the palbociclib-letrozole and letrozole alone groups, respectively (median: 37.5 months vs. 33.3 months; HR=0.81, 95% CI, 0.49-1.35; p=0.42). **PALOMA-2:** OS data were deemed immature at the time of data analysis. Median follow-up time was approximately 23 months; at this time point, the number of deaths was 133 (95 in the palbociclib-letrozole group and 38 in the placebo-letrozole group), which is 34% of the required events (no HR reported).	Is OS at just over two years reflective of longer-term survival? Why or why not?	The PALOMA-1 trial was too small to detect any meaningful OS results. However, there was a trend to improvement in median OS in the combination group. With sufficient follow-up in PALOMA-2, OS could be evaluated but any benefit may be confounded by post trial treatments.

Domain	Factor	Evidence and PAG input	Generalizability Question	CGP Assessment of Generalizability
Setting	Study Centres	**PALOMA-1:** the trial was conducted in 50 sites in 12 countries (France, Germany, Hungary, Ireland, Italy, Russia, South Africa, South Korea, Spain, Ukraine, and USA) including Canada. Enrolment by Country: Canada: n=5 (3%) US: n=31 (19%) Hungary: n=26 (16%) Germany: n=25 (15%) Ukraine: n=24 (15%) Ireland: n=18 (11%) Spain: n-15 (9%) Russian Federation: n=10 (6%) Korea: n=5 (6%) Italy: n=3 (2%) France: n=2 (1%) South Africa: 1 (<1%) **PALOMA-2:** the trial was conducted at 186 sites in 17 countries including Canada, USA, UK, Ireland, Belgium, France, Spain, Italy, Germany, Poland, Ukraine, Hungary, Russia, Korea, Japan, Taiwan and Australia.	Do the trial results apply to patients from Canadian centres? Are there any known differences in practice patterns between the countries listed and Canada?	Overall, most patients were from the US and Western Europe, where practice patterns would be similar to Canada. Differences in practice patterns, available therapies and access to care in other countries probably accounts for the high number of de novo metastatic cases included.
Abbreviations: ABC - advanced/metastatic breast cancer; **AIs** - aromatase inhibitors; **CGP** - Clinical Guidance Panel; **CI** - confidence interval; **ECOG** - Eastern Cooperative Oncology Group; **ER** - estrogen receptor positive; **HER2** - human epidermal growth factor receptor 2; **HR** - hazard ratio; **NMA** - network meta-analysis; **PAG** - Provincial Advisory Group; **PFS/TTP** - progression-free survival/time-to-progression; **PS** - performance status; **OS** - overall survival.				
Notes: [A]The subgroup of patients with bone only disease also included 29 patients; in this subgroup the treatment effect favoured the palbociclib-letrozole arm and was statistically significant.				

1.2.4 Interpretation

Burden of Illness and Need

Breast cancer is a common disease in women. Annually, approximately 22,500 cases (2015 figures) are diagnosed and 5,000 will die, usually after developing metastatic disease.[7] Of these, approximately 65-70% will have ER+ breast cancer and will be treated with targeted agents against estrogen.[8] This is an effective initial treatment and research has been directed to improve anti-estrogen or endocrine therapy to make gains in OS. In the first-line setting of ABC, improvement in PFS is often the goal of treatment as there are various subsequent lines of therapies available that can impact OS.

Effectiveness

PALOMA-1 was a small open-label phase 2 RCT that compared an established first-line endocrine therapy (letrozole) to letrozole given with palbociclib for post-menopausal women with ER+/HER2- ABC.[3] This was an international trial that globally accrued 165 patients. The trial demonstrated a statistically significant improvement in PFS from 10.2 months with letrozole alone to 20.2 months with combination therapy of palbociclib plus letrozole (HR=0.49; 95% CI, 0.32 to 0.75, one-sided p=0.0004). With an absolute improvement in PFS of 10 months, the magnitude of benefit is both statistically and clinically meaningful. There was no statistical difference in median OS between the two treatment groups; however, the trial was not powered to detect a significant difference in OS. Median OS was 37.5 months for palbociclib-letrozole versus 33.3 months for letrozole alone (HR=0.81; 95% CI, 0.49 to 1.35; two-sided p=0.42).

Preliminary results from PALOMA-2,[1,2] the larger confirmatory, double-blind, placebo-controlled randomized trial of PALOMA-1, confirmed that the primary endpoint of PFS was improved with the addition of palbociclib to letrozole compared to letrozole alone in the treatment of first-line ER+/HER2- post-menopausal ABC patients. This trial was presented at the American Society of Clinical Oncology in June 2016. PALOMA-2 showed similar benefits to PALOMA-1 in PFS. The trial randomized in a 2:1 study design, 666 women who did not receive any prior treatment for advanced disease and who were not resistant to AIs. The primary endpoint was investigator-assessed PFS. Secondary endpoints were ORR, OS, safety, and patient-reported outcomes. Baseline characteristics were similar to previous clinical trials for post-menopausal women, whereby the median age was 61-62 years (range 28-89) and around 40% had a disease-free interval from (neo)adjuvant endocrine therapy >12 months and only 22% were $\leq$12 months. Around 37% of these patients had de novo advanced disease with no prior therapy. The investigator assessment of PFS demonstrated a median PFS of 24.8 months with combination therapy compared to 14.5 months with letrozole alone, obtaining a HR of 0.58 (95% CI, 0.46 to 0.72; one-sided p<0.000001). As with PALOMA-1, this afforded a 10-month PFS benefit with combination palbociclib-letrozole compared to letrozole alone (odds ratio=1.55; 95% CI, 1.05 to 2.28; p=0.0132). All pre-defined patient subgroups benefited with the combination therapy. Objective response rate in patients with measureable disease, a secondary endpoint, showed a benefit of 55% with combined treatment compared to 44% with letrozole alone, and a clinical benefit response rate of 85% with combination palbociclib-letrozole compared to 70% with letrozole alone (OR 2.39%; p<0.0001). Due to the short follow-up of only 23 months, the median OS has not yet been achieved for this trial.

Safety

In PALOMA-1,[3] the most common grade 3 or 4 AEs were neutropenia (54% in the palbociclib-letrozole group versus 2% in the letrozole alone group), leucopenia (19% versus 0%), anemia (6% versus 1%) and fatigue (4% versus 1%). Despite the higher incidence of AEs seen in the combination group, there were only 13% who discontinued therapy due to AEs compared to 2% in the letrozole alone group. Although the most common side effects experienced with palbociclib-letrozole in this trial are not life threatening, they do require monitoring by an experienced health care team familiar with the toxicities associated with this combination, as a higher incidence of AEs (e.g., febrile neutropenia) may occur in an unselected non-clinical trial population. The only patient-reported outcome was pain, measured using the modified BPI-sf, to determine if there was a difference in myalgia or arthralgia with the addition of palbociclib to letrozole. No measured differences in pain were observed between the two treatment groups.[9] There were no reported QOL parameters in this trial.

In the PALOMA-2 trial,[1,2] safety and tolerability were similar to PALOMA-1, with grade 3 and 4 neutropenia being 55%, compared to <1% in the placebo-letrozole group. Overall incidence of serious AEs was higher in women receiving palbociclib-letrozole versus letrozole alone (19.5% versus 12.6%), with febrile neutropenia occurring in 1.6% of patients receiving palbociclib-letrozole compared to 0% with letrozole alone, and pulmonary embolism occurring in 0.9% of patients in the combination treatment group compared to 1.4% in the placebo-letrozole group. Permanent treatment discontinuation associated with AEs was higher in the combination treatment group at 9.7% compared to 5.9% in the placebo-letrozole group. Deaths due to AEs were higher in the palbociclib treatment group with 2.3% of patients compared to 1.8% in the placebo-letrozole group.

1.3 Conclusions

The CGP concluded that there is a net overall clinical benefit to the combination of palbociclib and letrozole compared with letrozole alone in the treatment of postmenopausal women with ER+/HER2- ABC who have not received any prior treatment for metastatic disease. This is based on the PALOMA-1 trial and the preliminary results of the PALOMA-2 trial. From a clinical perspective:

- Based on the preliminary results of PALOMA-2, a 10-month median PFS benefit was achieved, as was demonstrated in PALOMA-1. The median PFS was about four months longer in PALOMA-2 compared to PALOMA-1, for both the combination group and the placebo-letrozole group. This difference can be accounted for in PALOMA-2 since there was a larger patient population in this placebo-controlled RCT, and the PFS of 14.5 months demonstrated in the control group of letrozole alone was more comparable to previously reported clinical trials for AI first-line therapy in ER+/HER2- ABC. Both PALOMA-1 and PALOMA-2 had 49% and 37% of enrolled patients with de novo advanced disease with no prior anti-cancer therapy. This was estimated to be higher than what is typically seen in the Canadian context, with the de novo population in PALOMA-2 demonstrating a lower treatment effect in the combination group (HR=0.67), but still statistically significant. It is anticipated that the PALOMA-2 trial results will be published in a peer-reviewed journal. Finally, it is assumed based on submitted data that there was no detriment in QOL in patients treated in the combination treatment group compared to placebo-letrozole. This will also be confirmed once the peer-reviewed publication is made available.
- OS data in PALOMA-2 were immature at the time of data analysis. With sufficient follow-up, OS could be evaluated but any benefit may be confounded by post trial treatments.
- The PALOMA-1 trial did not enrol patients with an ECOG performance status of 2 and only 2% of patients enrolled in the PALOMA-2 trial had an ECOG performance status of 2. Therefore, the CGP cannot conclude there is benefit in patients with a performance status of 2. As most patients in clinical practice will have a performance status of 0 or 1, the CGP felt the combination of palbociclib with letrozole should be limited to these patients.
- It is important to note that the addition of palbociclib to letrozole in the treatment of first-line ER+/HER2- ABC patients will require closer clinical monitoring compared to letrozole alone, based on the safety and toxicity of combination treatment. Specifically, myelosuppression with neutropenia and a risk of febrile neutropenia was noted in PALOMA-2. Clinical medical education will be required of treating oncologists as to the AEs and appropriate monitoring and treatment of them when palbociclib is added to first-line letrozole therapy. This was previously noted from clinical experience from BOLERO-2 with the addition of everolimus to exemestane, where unexpected severe AEs were experienced in the clinical setting

and education with prophylactic treatment strategies were developed. Therefore, caution and clinical education will be required to ensure safe delivery of care of letrozole and palbociclib.

- The study design of PALOMA-1 and PALOMA-2 did not explore the role of combining palbociclib with other endocrine therapies. The CGP felt the combination of palbociclib with an AI should be limited to letrozole based on the current evidence.
- Within the Canadian context, based on the results of both PALOMA-1 and PALOMA-2, it is likely that the combination of palbociclib-letrozole will replace single agent first-line endocrine therapy in the metastatic setting. In the interim, based on the results of PALOMA-1 and PALOMA-2, it is possible the use of letrozole in the adjuvant setting for ER+ post-menopausal women may decrease, as prior use of letrozole may be a barrier to receiving the combination of letrozole and palbociclib in the advanced treatment setting. However, the decision of treatment choice of endocrine therapy in the adjuvant setting may be mitigated by allowing the treatment coupling of palbociclib with any endocrine therapy (tamoxifen, any AI, fulvestrant) in the treatment of first or second-line ER+/HER2- ABC patients. In fact, this is now allowed in the European Union, while recognizing that clinical evidence only exists for combining palbociclib with letrozole or with fulvestrant, based on the randomized trials of PALOMA-1, 2 and 3.
- At the time of this review, fully published data on palbociclib includes PALOMA-1 in addition to one phase 3 RCT, PALOMA-3, which assessed the clinical benefit of palbociclib in combination with another endocrine therapy, fulvestrant.[10] Palbociclib-fulvestrant was used as second-line therapy for ER+/HER2- post-menopausal ABC and therefore does not directly compare to PALOMA-1 and 2, but does provide clinical efficacy and safety data for this combination. The CGP noted that the combination of palbociclib plus fulvestrant as second-line therapy for ER+/HER2- post-menopausal ABC is out of scope of the current review.

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 with an estimated 25,000 women being diagnosed and an estimated 5,000 deaths in 2015.[7] While many women diagnosed with early stage breast cancer will be cured with treatment, some women will experience a relapse of their breast cancer (metastatic spread to other organs), with an additional 5-10% of women who will present with de novo metastatic breast cancer. Advanced or metastatic breast cancer (ABC) is not curative with an expected median life expectancy around 31 months.[11]

The goals of systemic therapy in women with ABC are to improve overall survival (OS) and or/ progression free survival (PFS) and to maintain and/or improve their quality of life. Systemic therapy may consist of endocrine therapy and/or targeted therapies and/or cytotoxic chemotherapy. The selection and sequencing of these therapies are dependent on several factors including: the biological characteristics of the breast cancer, tumour burden, involvement of vital organs, pace of the disease, performance status (PS), comorbidities of the patient, and patient's preference.

The most common type of breast cancer is estrogen driven, accounting for approximately 65 to 70% of all breast cancers that are estrogen receptor positive (ER+).[8] Selective therapies against the estrogen receptor (endocrine therapy) are an integral part of systemic therapy for both adjuvant (curative) and ABC. Tamoxifen, a selective estrogen receptor modulator, has shown to be effective in both pre-and post-menopausal women treated for ER+ ABC. Aromatase inhibitors (AIs) prevent the conversion of androstenedione to estradiol in peripheral tissues (e.g. fat, muscle, adrenals) in post-menopausal women and have also demonstrated clinical benefit with advanced endocrine sensitive disease. Non-steroidal AIs (letrozole and anastrozole) are commonly used as first-line agents in ER+ ABC. Similarly, fulvestrant, an estrogen receptor down regulator, has also been shown to be effective in this patient population.

Most estrogen-driven breast cancers will initially respond to endocrine therapy, but this response is unfortunately limited and the disease becomes resistant to endocrine manipulation and recurs (acquired resistance). Furthermore, there is a small group of ER+ ABC patients whose disease does not respond to first-line endocrine therapy and this is considered de novo or primary resistance. Improved understanding of the intracellular pathways involved in endocrine resistance led to identification of an intracellular target known as mTOR (mammalian target of rapamycin) and the approval of everolimus (an inhibitor of mTOR) for use with exemestane (a steroidal AI) in women whose disease has become resistant to first-line AI therapy.

Thus targeted therapy is starting to expand options for ER+ ABC, particularly in situations of primary or acquired resistance, and further understanding of intracellular signaling, including aberrant cell cycling in cancer cells, provides further opportunities to prevent or delay endocrine resistance and allow for longer treatments with endocrine therapy.

2.2 Accepted Clinical Practice

The treatment of ABC consists of systemic therapy (including endocrine therapy, chemotherapy and targeted therapies), supportive therapies (e.g. bone-modifying agents for bone metastases, analgesics, anti-nausea agents), radiation therapy, surgery and access to a palliative care and allied health care team (e.g. dietitian, social worker). The choice of systemic therapy and overall treatment will depend on the biological characteristics of the breast cancer, the patient's comorbidities and preferences, physician recommendations and the availability of treatment options.

While there is no standard treatment algorithm for ER+ ABC, it is recommended that endocrine therapy be considered the first-line treatment of choice in women, with the exception if there is evidence of visceral crisis (compromised organ function due to metastatic disease). In the presence of visceral crisis and/or rapidly progressive symptomatic disease, it is recommended to initiate therapy with cytotoxic chemotherapy to rapidly decrease the tumour burden to improve visceral organ function and improve symptoms. Endocrine therapy for ER+ ABC consists either of tamoxifen, aromatase inhibitors or fulvestrant. Sequencing of these agents varies and can be driven by therapies used in the adjuvant setting, disease-free interval and patient tolerability. Despite the clinical efficacy of these agents, resistance to this treatment is inevitable thereby limiting the effectiveness of them in subsequent lines of treatment. Understanding the mechanisms of endocrine resistance has led to the identification of aberrant intracellular signaling of through the PI3K-Akt-mTOR signaling pathway. Blocking this pathway specifically with everolimus (mTOR inhibition) demonstrated improvements in median PFS in combination with exemestane (an AI) in ER+ ABC patients who demonstrated endocrine resistance. The combination of everolimus and exemestane is now considered standard therapy in the sequencing of endocrine therapy for ER+ ABC.[12]

In addition to understanding signaling pathways involved in endocrine resistance, it has been well recognized that dysregulation of the cell cycle is one of the defined hallmarks of cancer, including breast cancer. Aberrant cell cycling is affected by several genetic alterations in key cell cycle regulatory proteins. These consist of cyclin-dependent kinases (CDKs), which are a large family of serine threonine kinases that together with their regulatory protein partners, the cyclins, regulate and control progression through the cell cycle. Mutational changes in the genes controlling these cell cycle regulatory proteins have led to aberrant cell cycling, rapid cellular division and subsequently tumour and cancer cell growth. Targeting these regulatory proteins and inhibiting their action may provide another therapeutic target to control cell division. Palbociclib, a reversible, oral, small molecule inhibitor of cyclin dependent kinases 4 and 6 (CDK4/6) stops the progression through the cell cycle from G1/S when partnered with cyclin D. CDK4/6 and cyclin D play a crucial role in the regulation of the G1/S transition of the cell cycle through regulation of the phosphorylation of pRB (retinoblastoma protein), a key driver of the cell cycle. By inhibiting CDK4/6, pRB is not hyperphosphorylated by CDK4/6-cyclin D and the cell cycle is arrested (halted) in G1. Pre-clinical in vitro studies demonstrated that in tamoxifen-resistant cell lines, the addition of palbociclib in combination with tamoxifen demonstrated synergy in overcoming endocrine resistance.[13]

Pre-clinical findings prompted the PALOMA series of clinical trials examining the safety and efficacy of palbociclib combined with other endocrine therapy in both first-line (PALOMA-1 and PALOMA-2) and second-line (PALOMA-3) treatment of ER+, human epidermal growth factor receptor negative (HER2-) ABC. The potential benefit of combining palbociclib with endocrine therapy as first-line treatment is the focus of this review.

2.3 Evidence-Based Considerations for a Funding Population

The evidence-based population suitable for consideration of palbociclib for the first-line treatment of ER+ ABC would be the same population included in the clinical trial PALOMA-1 and the most recent primary analysis of the larger double-blind phase 3 PALOMA-2 clinical trial. This would include post-menopausal women with ER+, HER2- ABC who had not received any prior systemic treatment for their advanced disease. Patients were excluded if they had received letrozole as either neoadjuvant or adjuvant treatment within the 12 months prior to study entry, had received any previous treatment for ABC, had brain metastases, or had previously been treated with a CDK inhibitor. Patients had a good performance status (ECOG PS 0-1). Treatment with palbociclib ± letrozole continued until disease progression, unacceptable toxicity or patient/physician recommendation.

It is likely that following the combination of first-line therapy of palbociclib and letrozole, further endocrine therapy will be considered for second- or third-line including exemestane and everolimus.

2.4 Other Patient Populations in Whom the Drug May Be Used

Currently, the use of palbociclib with letrozole should be considered as first-line combination endocrine-targeted therapy. However, data from PALOMA-3 suggests second-line sequencing with palbociclib and fulvestrant may be another therapeutic option in women not eligible for palbociclib therapy in first-line (e.g. recurrence on adjuvant letrozole therapy or recurrence within 12 months of stopping adjuvant letrozole).[10]

There are no data to support the use of palbociclib and letrozole in patients with brain metastases or those with ER+, HER2+ ABC (not included in the PALOMA-1 or PALOMA-2 trial populations). Further studies are warranted in these patient populations.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, Rethink Breast Cancer (Rethink) and Canadian Breast Cancer Network (CBCN), provided input on the palbociclib (Ibrance) resubmission for the treatment of HER2-negative advanced breast cancer for those who have not received previous systemic treatment for their advanced disease.

CBCN in collaboration with Rethink conducted an online survey of metastatic breast cancer patients and caregivers in 2012 (2012 Survey). Patients were contacted through the membership databases of CBCN and Rethink. Seventy-one (71) patients and sixteen (16) caregivers participated in the survey. None of the patients who participated in this survey had experience with the treatment under review. Questions in the survey included a combination of scoring options and free form commentary.

In addition, CBCN conducted telephone interviews with three patients from the USA who had direct experience with the treatment under review, as CBCN indicated there were no Canadian patients available to discuss their direct experience on the treatment under review because the treatment under review is not for sale in Canada. CBCN also reviewed additional print sources, including current studies and grey literature to identify issues and experiences that are commonly shared among many women living with breast cancer in order to provide supporting context.

Rethink also conducted online and telephone interviews with four patients that have direct experience with the treatment under review. There was also input provided from testimonials from patients who have experience with palbociclib from Team Inspire, an organization that builds online health and wellness communities for patients and caregivers.

From a patient's perspective, managing a diagnosis of metastatic breast cancer is challenging, as current treatment options for metastatic breast cancer are only effective at prolonging progression-free disease, and most cases of advanced disease will progress and symptoms will worsen. Rethink and CBCN indicated that the many effects of metastatic breast cancer represent a significant or debilitating impact (both physical and social) on patients' and caregivers' quality of life. Both Rethink and CBCN reported that current treatment options and effectiveness vary among type of cancer, location of cancer, and how symptoms are experienced. Respondents expressed concerns with the side effects and tolerability of traditional chemotherapy regimens. According to Rethink and CBCN, patients' expectations for the new treatment under review are the following: (1) to delay the progression of the disease, (2) to relieve cancer-related symptoms, and (3) to improve on quality of life. Respondents who have experience with palbociclib reported that the treatment helped to stabilize and control their disease. Respondents also reported their ability to live life productively. The key adverse effects experienced by these respondents included: low white blood cell count, fatigue, febrile neutropenia, hair thinning, runny nose, mouth sores, and diarrhea. Out of the seven respondents with experience with palbociclib, most respondents were able to tolerate these side effects, while others had to reduce their dosage of palbociclib. Respondents commented on the ease of the oral dosage and appreciated having a break of one week on the treatment.

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients Have with HER-2 negative advanced breast cancer

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

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

In the 2012 Survey, patients were asked what physical impact cancer related symptoms had on their quality of life. Key responses reported by the respondents:

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

Rethink also reported on other physical symptoms identified by patients that included: early menopause, mood swings, loss of appetite, neuropathy, loss of balance, incontinence, and skin bruising.

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

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

Both Rethink and CBCN also reported on the financial burden associated with living with breast cancer and how it extends far beyond any loss of income during a temporary or permanent absence from employment. CBCN and Rethink stated that in addition to the loss of income during illness, breast cancer patients can also incur substantial costs associated with treatment and disease management.

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

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

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

3.1.2 Patients' Experiences with Current Therapy for HER-2 Negative Advanced Breast Cancer

Both CBCN and Rethink reported that the goals of current treatment options for metastatic breast cancer include controlling the progression of the disease (extending life), and reducing cancer-related symptoms (extending or stabilising quality of life). They also submitted that treatment options and effectiveness may vary among type of cancer, location of cancer, and how symptoms are experienced.

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

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

- Approximately two-thirds of respondents indicated that when it comes to fatigue, nausea, depression, problems with concentration, memory loss, diarrhea and insomnia, some or a moderate impact on one's quality of life would be considered acceptable, and approximately one quarter of respondents indicated that a strong or debilitating impact would be considered acceptable.
- 70% of respondents indicated that when it comes to pain, some or a moderate impact on one's quality of life would be considered acceptable, and 27% of respondents indicated that a strong or debilitating impact would be considered acceptable.

Rethink indicated that respondents made two observations which place limitations on this statistical data. These were based on comments provided in the open-ended portion of the survey section.

1. Some patients felt they did not understand the wording of the question

2. Some patients felt they lacked capacity to respond to a hypothetical question of this nature.

Below were key responses from respondents from the survey:

"*My preference is for access to lots of treatments so I can live for long time. Less side effects are preferable, but if there is no option I will put up with symptoms of treatment in order to live longer."*

"Not all patients suffer the same way.[…] It was a difficult task to answer that question."

The following were the responses noted when respondents were asked about their willingness to tolerate risk with a new treatment.

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

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

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

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

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

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

- Among patients with children or other dependents, 53% indicated that there is minimal or no access to appropriate care for their loved ones when they are experiencing debilitating symptoms related to their cancer, and 40% identified barriers to accessing quality care during cancer treatment. In addition, 26% of patients indicated that there are minimal or no transportation options in their community when they seek treatment and support for symptoms. Likewise, 18% indicated a serious lack of adequate transportation options to access cancer treatment. One respondent indicated that in a rural community, it is difficult to get to the hospital in the winter months.

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

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

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

CBCN and Rethink received input from 16 caregivers who participated in the 2012 survey. According to Rethink and CBCN, caregivers experience a significant negative impact on their quality of life. Caregivers reported experiencing a number of symptoms of stress, as well as a negative impact on their ability to continue their daily routines, responsibilities, and self-care for personal health issues. Both CBCN and Rethink also noted the physical, social and financial impact of caregiving for someone with metastatic breast cancer.

In regards to the physical impact of caregiving for someone with metastatic breast cancer, the following responses were noted among the participants of the 2012 survey.

- 77% of caregivers indicated that anxiety, fatigue, and problems with concentration had a negative impact on their quality of life.
- 67% of caregivers indicated that depression and insomnia had a negative impact on their quality of life.
- 55% of caregivers indicated that memory loss and physical pain such as muscle tension had a negative impact on their quality of life.

In regards to the social and financial impact of caregiving for someone with metastatic cancer, CBCN and Rethink reported that all caregivers stated that their role has resulted in a negative impact on their personal, social, and professional lives. The following responses were noted among the participants of the survey.

- 100% of caregivers identified restrictions to their employment, their ability to pursue personal interests and hobbies, their ability to travel, and their ability to exercise. One respondent indicated that there was a clear impact on his or her ability to fulfill his job responsibilities and negatively impacted on his or her career progression
- 89% of caregivers identified restrictions to their ability to participate in social events and activities
- 75% of caregivers identified restrictions to their ability to volunteer
- 67% of caregivers identified restrictions to their ability to spend time with loved ones; and
- 44% of caregivers identified restrictions to their ability to care for children and dependents.

In particular, one respondent stated: *"I do not want to be a burden on my family. I would not want my family to decline/lose good opportunities in their careers & restrict them in anyway on my behalf/condition."*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations and Experiences with palbociclib.

According to Rethink, because this indication is in the first-line setting of care for ER positive, HER2 negative metastatic breast cancer patients, almost all have not had a therapy to compare it to in this setting. Some respondents did compare it to other therapies in general from earlier stages. CBCN and Rethink stated that some respondents interviewed said that this therapy is much easier than others including traditional chemotherapy.

Rethink also reported upon adverse effects/effectiveness of the current therapy. Rethink stated that every respondent they spoke to for this submission clearly indicated that the toxicities were mild and no one discontinued taking this combination because of toxicities. Overall, patients are willing to accept adverse effects for PFS and quality of life.

Both CBCN and Rethink also reported upon the impact and value to patients. In particular, it was very important for patients to have quality of life when receiving treatment for metastatic disease. Respondents reported the importance to have the energy to attend children's activities and to spend time with family and friends.

None of the respondents who participated in the 2012 survey had experience with palbociclib.

Notwithstanding, CBCN was able to find three US patients with various levels of experience with palbociclib. Rethink also conducted interviews with four patients who have direct experience with palbociclib.

Below are the reported details from the three respondents who were interviewed by CBCN.

- Patient 1: Has been on treatment since September 10, 2015 and is accessing prescribed treatment.
- Patient 2: Has been on treatment for two years, and originally began accessing treatment through clinical trials.
- Patient 3: Has been on treatment since February 18th, 2015 and is accessing prescribed treatment.

According to CBCN, all three patients expressed their personal satisfaction with the treatment and Patients 2 and 3 specifically noted that their oncologists are pleased with palbociclib's efficiency in stabilizing and controlling their disease. CBCN reported that all three respondents discussed their ability to live life productively, with an excellent quality of life.

The following quotations have been excerpted from these respondents to further illustrate their perspectives.

- "*I have a very good quality of life with this treatment compared with my previous treatments of chemotherapy. I was unable to work for 2 years during and after the chemotherapy, and this treatment has allowed me to continue working at a fairly physically demanding job which is very important to me. The side effects of*

this treatment haven't had a significant impact on my life and I am able to continue on with most of my regular activities." –Patient 1

- "*Access to this treatment means the world to me. I have a daughter that I have to live for, and the Ibrance has been helping me for the last two years, allowing me to live my life as normally as possible. I am able to be involved in my daughter's daily life with no limitations on my quality of life* " -Patient 2
- "*My doctor actually just lowered my dose because my numbers were very good and I was able to tolerate the Ibrance well*." –Patient 3

Rethink also reported similar findings with regards to the quality of life. One respondent stated "*My quality of life is amazing. If I didn't know I had cancer, I wouldn't know I had cancer…that's how good I feel. I am optimistic that I will live at least several years before the cancer progresses and some other therapy will be considered*." Another respondent stated: "*My tumor has shrunk from 10cm to just under 3cm in a short time*." A third respondent indicated "*My beginning tumor marker was 181 (under 35 normal range) and at the end of the first month it went down to 113 - now at 94*."

In regards to assessing risks associated with treatment, CBCN reported that the respondents were well aware of the possible risks of this treatment and were made aware that all patients can respond differently to side effects. In addition, all three respondents expressed that they found the side effects, including febrile neutropenia and fatigue to be tolerable and manageable through dosage adjustments and support medications. Patient 3 expressed that she was very fortunate to be have experienced only minimal side effects on the treatment, while Patient 1 stated she was able to continue on with most of her regular activities.

According to CBCN, Patient 3 stated: *"My productivity has not been impacted by this treatment. I'm still able to work, be a mom, a wife and I continue to be very involved with my Jewish community. I know I am very fortunate, especially as many people are not so lucky with side effects*."

The following responses below were provided by the CBCN respondents regarding adverse effects and symptoms.

- "*I was given Neupogen which has been successful in managing the neutropenia, my dose of Ibrance also been reduced from 125mg to 100mg which is managing the neutropenia as my white blood cell count hasn't dropped drastically.*" –Patient 1
- *"I find the side effects to have minimal impact on my life, especially because I'm able to access support treatments for my FN.*"-Patient 2
- "*All of my side effects have been acceptable to me, because the treatment is working for me. I am still able to live my productive life, so I feel very lucky to be on a treatment that is working."* –Patient 3

Of the respondents who were interviewed by Rethink and who shared their experience with Team Inspire, the majority experienced low white blood cell count. Some respondents were able to tolerate it and others had to reduce their dosage of palbociclib. Other mild adverse effects from this group included: fatigue, hair thinning, runny nose, mouth sores, and diarrhea. One respondent stated: "*I have had very few side effects and have continued my active lifestyle. With the Ibrance, my TM have gone from 181, to 119, to 91. I'm pleased with the progress on this medication.*"

Rethink indicated that the majority of respondents will tolerate these side effects because the effectiveness of this treatment has been very positive. Rethink reported that none of the four respondents had to suspend the use of palbociclib because of side effects. Some did lower the dose, but even at the lower dose, it had no effect on progression (up to this point in treatment).

Respondents were also asked by CBCN about the impact of drug administration. They commented on the ease of the oral formulation and appreciated having a break of one week on the treatment.

In regards to treatment alternatives, CBCN reported that both Patients 1 and 2 mentioned that without this treatment, they would have been left with only chemotherapy as an alternative treatment, and both respondents expressed concerns with the side effects and tolerability of extensive chemotherapy regimens.

The following excerpts further help to illustrate their perspectives on treatment alternatives.

- *"Compared to the chemotherapy the side effects from this treatment are much more tolerable. The side effects of the chemo were, loss of hair, extremely painful finger and toenails that were pulling away from the nail bed, neuropathy in my feet and bleeding noses. I wasn't able to work for 2 years after the chemo but I have been able to work through this treatment"* –Patient 1
- *"If I was not on Ibrance, I would likely had to have chemotherapy, but I have serious concerns about the side effects of chemo and how that would impact my life every day.* " –Patient 2

CBCN stated that Patient 3 discussed that her alternative option would have been to try an aromatase inhibitor, however she expressed that her previous experience on this type of treatment had left her with some discomfort. As stated by patient 3, "*I would probably be on an AI, but when I was previously just on letrozole I had major joint discomfort, which was very painful to live with, so I'm very happy to have other options available to me.* "

Respondents who were interviewed by CBCN and Rethink also commented on access to palbociclib.

The following were some of the key responses reported.

- "*In terms of my medical condition, having access to this means I have my best fighting chance of fighting this for as long as possible. Ibrance is a milestone in medicine to me. Knowing that I am privileged to be on this treatment, means I actually have a chance of living well for as long as possible. I aspire to be like the women I know who have no evidence of disease and I feel that because I had access to Ibrance, because I was given my best fighting chance. It also means that I can free the person from the patient. I don't want this disease to define who I am, and having access to Ibrance has allowed me to do that. This diagnosis is so shocking, and you have to make all these decisions about your health as just a "patient" and now I am finally able to live with this disease and be proactive about it. But I'm not defining myself like that anymore, I'm back to being a full person."*
- "*I was so devastated when the initial diagnosis occurred and was so discouraged to think about having chemo treatments like I had originally. I am so happy I sought a second opinion and his recommendation was for Letrozole and Ibrance. It had just*

been approved internally at the Oncology clinic the day I came for my second opinion and I was apparently an ideal candidate."

- "*It means that I can go a much longer time before developing more mets, while maintaining a relatively normal life style*."

Additionally, Rethink noted that respondents reported notable effectiveness with the treatment. One respondent stated "*My tumor has shrunk from 10cm to just under 3cm in a short time*." Another respondent indicated that "*My beginning tumor marker was 181 (under 35 normal range) and at the end of the first month it went down to 113 - now at 94*".

As one woman living with metastatic breast cancer put it, *"we need as many tools in our tool box to fight this disease, when one tool breaks we need another one that will do the job."*

3.3 Additional Information

Rethink would like to state that palbociclib has received FDA and Health Canada approval and has demonstrated positive experience from both clinical trials and women who are currently taking this line of therapy. Rethink submitted that they know of at least one patient who successfully gained access to palbociclib through private insurance coverage which clearly demonstrates that there are insurers who are not uncertain of the clinical benefit of palbociclib and are putting patients first.

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

Clinical factors:

- Generalizability of PALOMA-2 trial to palbociclib in combination with other aromatase inhibitors
- Data on use in patients who have failed other aromatase inhibitors
- Monthly monitoring and bloodwork for neutropenia, which is not required with letrozole monotherapy

Economic factors:

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

Please see below for more details.

4.1 Factors Related to Comparators

Various aromatase inhibitors are available for initial treatment of metastatic disease in estrogen-receptor positive, HER-2 negative breast cancer. These include anastrozole, exemestane and letrozole. PAG noted that the PALOMA-1 and PALOMA-2 trials compare palbociclib plus letrozole to letrozole alone. PAG is seeking comparative data to other aromatase inhibitors.

4.2 Factors Related to Patient Population

PAG noted that this is a large patient population.

If recommended for funding, PAG is seeking guidance on the appropriateness of adding palbociclib for patients who are already on letrozole but not yet progressed or switching patients who are already on other aromatase inhibitors but not yet progressed to palbociclib plus letrozole.

PAG is seeking for information on the generalizability of data for the use of palbociclib in combination with other aromatase inhibitors.

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

If recommended for funding, PAG recognizes that treatment algorithms and eligibility criteria of other therapies may need to be re-evaluated.

Lastly, PAG noted that the results of the PALOMA-3 trial for palbociclib in combination with fulvestrant was published in 2015. However, the PALOMA-3 trial is for patients with endocrine resistant metastatic disease. PAG identified the PALOMA-3 trial would be out of scope of the current review for initial endocrine treatment for advanced disease.

4.3 Factors Related to Dosing

Palbociclib is taken daily for 21 days followed by 7 days off while letrozole is taken daily continuously. PAG has concerns that the dosing of palbociclib being different than letrozole may cause confusion for some patients and there is a risk of dosing error.

4.4 Factors Related to Implementation Costs

PAG noted that additional health care resources may be required to monitor and treat toxicities and monitor drug-drug interactions. Specifically, PAG noted that patients on letrozole are not seen by oncologists on a monthly basis. However, due to the high incidence of neutropenia with the addition of palbociclib, patients will need to be seen monthly for monitoring and bloodwork.

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

The availability of three different strengths facilitates dose adjustments as the tablet 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.

4.5 Factors Related to Health System

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.

4.6 Factors Related to Manufacturer

PAG noted that palbociclib is packaged in bulk bottles of 21 day supply and have indicated that unit dose packaging would minimize exposure to health care professionals and patients.

PAG indicated that a new submission for palbociclib and fulvestrant would be required for funding consideration of the PALOMA-3 trial.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were received from two oncologists.

Based on available data, the oncologists providing input noted that palbociclib plus letrozole have added benefits over letrozole monotherapy. However, it was noted that there is no overall survival benefit data available and that there are added toxicities of palbociclib not seen with letrozole monotherapy.

Please see below for a summary of specific input received from the registered clinicians.

5.1 Current Treatment(s) for this Type of Cancer

The oncologists providing input noted that current treatment is usually either an aromatase inhibitor alone (letrozole, anastrozole or exemestane) or single agent palliative chemotherapy (either paclitaxel or capecitabine).

5.2 Eligible Patient Population

The oncologists providing input indicated that this is a common disease circumstance and thus the incident population will be relatively high.

5.3 Identify Key Benefits and Harms with New Drug Under Review

One oncologist advised caution with palbociclib and letrozole combination, given the lessons learned from combination therapy with exemestane and everolimus - where in practice this combination is very toxic and many patients were harmed. Due to the toxicities, he noted that many oncologists have stopped using exemestane and everolimus in combination or started everolimus at a lower dose than in the trial. He pointed to subsequent papers by Pond and Tannock that have raised significant issues with the trial publication which showed exemestane and everolimus combination was better than exemestane alone but noted that the difference is not as great as originally reported and despite the initial optimism, there is still no survival benefit.

This previous experience with exemestane and everoliumus combination is important – the wave of enthusiasm driving palbociclib and letrozole combination needs to be calmed down as there are no long-term safety data and no survival benefit. It was noted that

1. Palbociclib plus letrozole (or fulvestrant) will be more toxic than initially published in trials
2. The combination is very expensive
3. **There is no survival benefi**t published – it is not satisfactory to approve an agent thinking this may happen in the future as experienced with everolimus
4. The FDA data with the letrozole plus palbociclib trial showing the patients with bone metastasis were taken off study much earlier if they were on letrozole alone. This was an open label study and the effect was driven by physicians

knowing what treatment patients were on. This makes the combination look better than it is but radiology review showed no difference in bone response.

5. We could be left in a position of having two very expensive combination regimens both of which are toxic.

So in summary, the clinician providing input feels that we need to lean from the exemestane and everolimus experience. If palbocilib plus letrozole is approved, then Pfizer should immediately fund a population based study to open immediately that will collect data on who is getting treated, how long they respond for, toxicity etc.

So while running the risk of sounding like the voice of concern while others sing the praises of this agent – we need to caution our behaviour to maximally benefit our patients and protect the Health Care system from another potentially very expensive and toxic therapy.

5.4 Advantages of New Drug Under Review Over Current Treatments

One oncologist identified that the benefits to this patient population are substantial. He noted that chemotherapy can be toxic and detrimental to quality of life, yet single agent aromatase inhibitors have modest activity (though often durably). The hazard ratio for PFS with this new combination is striking and, though OS may be affected by downstream treatments, we would expect a better overall trajectory of disease (symptoms, QoL and postponement of chemotherapy need) by achieving longer term control and delay of progression. He feels that the toxicities of treatment are predictable and manageable, limited in duration (if discontinued) and would be acceptable to most patients given the benefits.

5.5 Sequencing and Priority of Treatments with New Drug Under Review

One oncologist providing input indicated that response rate benefits may translate to improved symptom control early in therapy and noted that the main advantage will be the longer disease control, deferring the need for subsequent less effective and more toxic lines of therapy.

It was also identified that optimal sequencing is unknown, in particular with the current treatment combination exemestane/everolimus and noted that chemotherapy is often “overkill” in this population given indolent nature of disease.

5.6 Companion Diagnostic Testing

None.

5.7 Additional Information

None.

6 SYSTEMATIC REVIEW

6.1 Objectives

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

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.

- Critical appraisal of a network meta-analysis comparing palbociclib with other therapies as first-line treatment in post-menopausal women with ER+ and HER2- ABC.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 3: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs	• Post-menopausal women (≥18 years) with ER+ and HER2- ABC not amenable to surgery (locally recurrent or metastatic disease) • Treatment naïve (no previous treatment for advanced/metastatic disease)	Palbociclib plus endocrine therapy Endocrine therapy can include: • Aromatase inhibitors (e.g., letrozole, anastrozole, exemestane) • Estrogen receptor downregulators (e.g., fulvestrant) • Selective estrogen receptor modulators (e.g., tamoxifen)	Endocrine therapy alone	**Progression-free survival** Overall survival Objective response rate Duration of response Clinical benefit** **Patient-reported outcomes** **QOL** **Adverse events**

Abbreviations: ABC - advanced/metastatic breast cancer; **ER** - estrogen receptor; **HER2** - human epidermal growth factor receptor 2; **QOL** - quality of life; **RCTs** - randomized controlled trials.

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

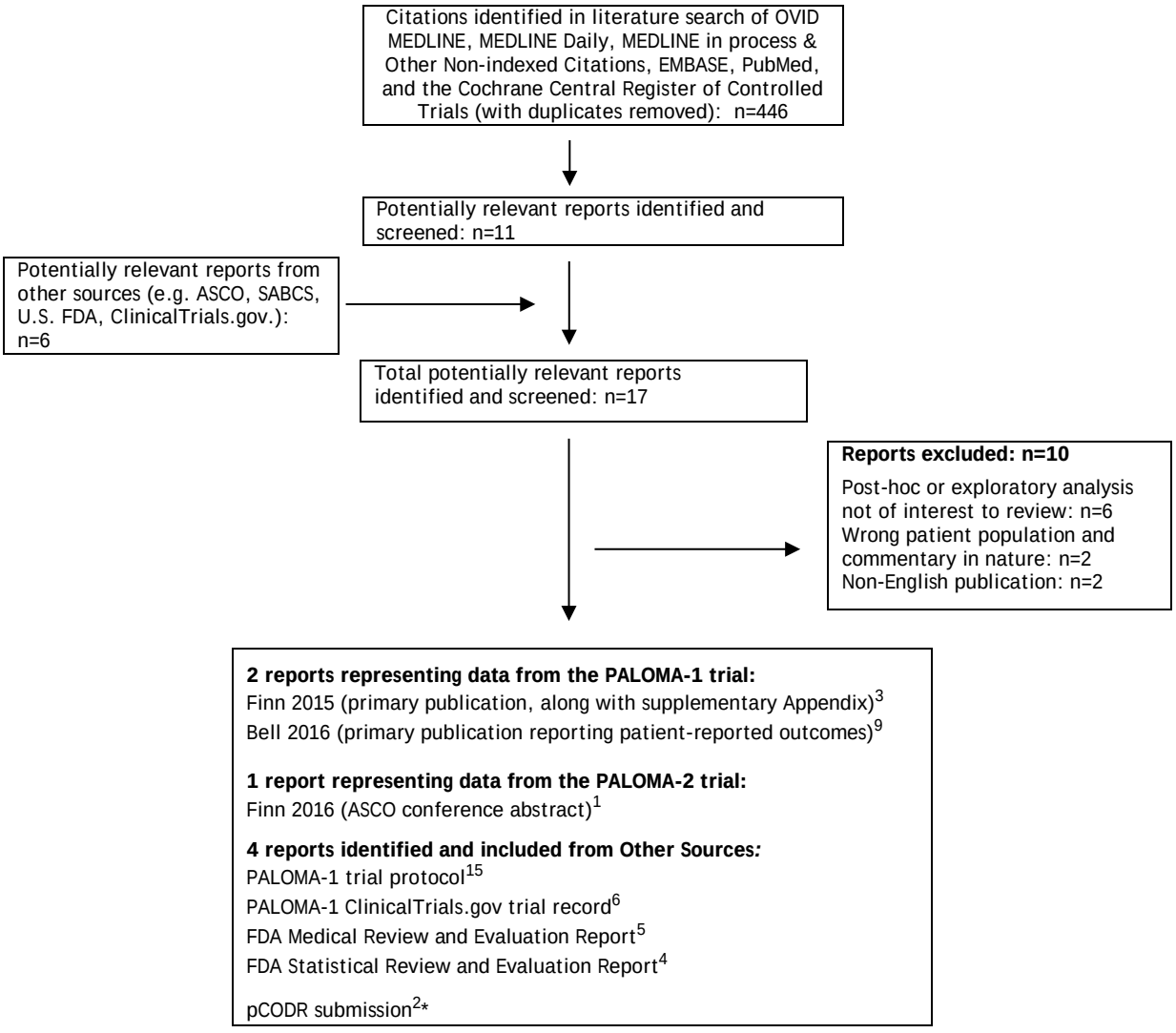
***Defined as the sum of complete and partial response and stable disease for 24 weeks or more.*

6.3 Results

6.3.1 Literature Search Results

Of the potentially relevant reports identified for full text review (n=17), seven reports were included in the pCODR systematic review[4-6,9,14,15] and ten reports were excluded. Reports were excluded from the review for the following reasons: they were either post-hoc or exploratory analyses of trial data not of interest to this review,[14,16-20] they were the wrong patient population and also commentary in nature,[21,22] or were only published in a language other than English.[23,24]

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



Note: Additional data related to the PALOMA trials were also obtained through requests to the Submitter by pCODR.

6.3.2 Summary of Included Studies

Two randomized controlled trials (RCTs), PALOMA-2[1,2] and PALOMA-1,[3] were identified that met the eligibility criteria of this review. The key characteristics of the trials are summarized in Table 4 and specific aspects of trial quality are summarized in Table 5. At the time this report was completed the PALOMA-1 trial was published and the PALOMA-2 trial was only available in abstract form; therefore, the majority of PALOMA-2 data summarized in this report comes directly from documents provided by the Submitter.[2]

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of key trial characteristics of the included PALOMA trials evaluating palbociclib combined with letrozole as first-line treatment in post-menopausal women with ER-positive and HER2-negative advanced or metastatic breast cancer.

Trial Design	Eligibility Criteria	Intervention	Comparator	Outcomes
PALOMA-2[1,2]				
Phase 3, double-blind RCT (2:1 ratio) Patient enrolment: February 2013 to July 2014 Data cut-off date: February 26, 2016 N randomized=666 N treated=666 Multicentre (186 sites in 17 countries including Canada) Randomization stratified by: • Disease site (visceral vs. non-visceral)[A] • Disease-free interval from end of (neo)adjuvant treatment to recurrence (≤ 12 months vs. >12 months vs. de novo advanced disease) • Prior (neo)adjuvant treatment received (prior HT vs. no prior HT) Funded by Pfizer	<u>Key Inclusion Criteria:</u> • Age ≥ 18 years • ER-positive • Locally recurrent disease not amenable to curative surgery or RT or evidence of metastatic disease • Measurable disease by RECIST version 1.1 or bone-only disease[C] • ECOG 0 to 2 • Adequate organ and marrow function • Available tumour tissue <u>Exclusion Criteria:</u> • Previous treatment for advanced disease • Prior (neo)adjuvant treatment with letrozole or anastrozole with disease recurrence while on or within 12 months of completing treatment • Previous treatment with any CDK inhibitor • Patients with advanced symptomatic visceral spread • Active uncontrolled or symptomatic CNS metastases, carcinomeningitis or leptommeningeal disease	Palbociclib (oral 125 mg once daily for 3 weeks, one week off in 28-day cycle) + Letrozole alone (oral 2.5 mg once daily) Treatment until disease progression, symptomatic deterioration, unacceptable toxicity, death or withdrawal of consent.	Placebo (oral once daily for 3 weeks, one week off in 28-day cycle) + Letrozole (oral 2.5 mg once daily)	<u>Primary</u>: • Progression-free survival (investigator assessed) <u>Key Secondary</u>: • Overall survival • Objective response (RECIST version 1.1) • Duration of response • Disease control (sum of CR and PR and stable disease ≥ 24 weeks) • QOL (FACT-B, EQ-5D) • Safety
PALOMA-1[3]				
Phase 2, open-label RCT (1:1 ratio) Patient enrolment: December 2009 to May 2012	<u>Key Inclusion Criteria:</u> • Age ≥ 18 years • ER-positive • Locally recurrent disease not amenable to surgery	Palbociclib (oral 125 mg once daily for 3 weeks, one week off in 28-day cycle)	Letrozole alone (oral 2.5 mg once daily)	<u>Primary</u>: • Progression-free survival (investigator assessed)

Trial Design	Eligibility Criteria	Intervention	Comparator	Outcomes
Data cut-off date: November 29, 2013 N randomized=165 N treated=160 Multicentre (50 sites in 12 countries) Randomization stratified by: • Disease site (visceral, bone or other) • Disease-free interval (>12 months from adjuvant treatment to recurrence vs. ≤ 12 months from adjuvant treatment to recurrence, vs. de novo advanced disease) Sequential Cohort design[B] • Cohort 1 (ER-positive and HER2-negative status) • Cohort 2 (CCND1 amplification, loss of p16 or both) Funded by Pfizer	or evidence of metastatic disease • Measurable disease by RECIST version 1.0 or bone-only disease • ECOG 0 or 1 • Adequate organ function <u>Exclusion Criteria:</u> • Previous treatment for advanced disease • Received letrozole as neoadjuvant or adjuvant treatment within 12 months of study entry • Received previous treatment with CDK inhibitor • Brain metastases	+ Letrozole alone (oral 2.5 mg once daily) Treatment until disease progression, unacceptable toxicity, study withdrawal or death.		<u>Key Secondary</u>: • Objective response (RECIST version 1.0) • Clinical benefit (sum of CR and PR and stable disease ≥ 24 weeks) • Duration of response • Overall survival • Patient-reported outcomes (modified BPI-short form) • Safety

Abbreviations: BPI - Brief Pain Inventory; **CCND1** - amplification of cyclin D1; **CDK** - cyclin-dependent kinases; **CR** - complete response; **ECOG** - Eastern Cooperative Oncology Group; **ER** -estrogen receptor; **EQ-5D** - EuroQOL- 5 Dimensions; **FACT-B** - Functional Assessment of Cancer Therapy - B questionnaire; **HER2**- human epidermal growth factor receptor 2; **HT** - hormone therapy; **PR** - partial response; **RCT** - randomized control trial; **RECIST** - Response Evaluation Criteria in Solid Tumors; **RT** - radiotherapy; **vs.** versus.

Notes:

[A] Visceral refers to any lung (including pleura) and/or liver involvement; non-visceral refers to absence of lung (including pleura) and/or liver involvement.

[B]Patients were enrolled and randomized in two separate but sequential Cohorts. In Cohort 1 patients were enrolled based on ER-positive and HER2-netative status only. In Cohort 2 patients were also required to have amplification of CCND1, loss of p16 or both.

[C] Tumour lesions previously irradiated or subjected to other locoregional therapy were only deemed measurable if disease progression at the treated site after completion of therapy was clearly documented.

Table 5: Select quality features of the included PALOMA trials evaluating palbociclib combined with letrozole as first-line treatment in post-menopausal women with ER-positive and HER2-negative advanced or metastatic breast cancer.

Trial	Treatment vs. Comparator	Primary Outcome	Required Sample Size	Sample Size	Randomization Method	Allocation Concealment	Blinding	ITT analysis	Final Analysis	Early Termination	Ethics Approval
PALOMA-2[1,2]	Palbociclib + letrozole vs. placebo + letrozole	Investigator assessed PFS	650 patients required for 347 PFS events to provide 90% power to detect an HR=0.69 using a one-sided alpha=0.025.[A] *Interim analysis:* Performed at 236 PFS events (approximately 68% of total events) to assess efficacy and early stopping for futility, potential sample size adjustment, and safety.[B]	444 vs. 222	Central IRT, stratified[C]	Yes	Yes[D]	Yes	Yes	No	Yes
PALOMA-1[3]	Palbociclib + letrozole vs. letrozole alone	Investigator assessed PFS	*Initial:*[E] 150 patients required in Cohort 2 for 114 PFS events to provide 80% power to detect an HR=0.67 using a one-sided alpha=0.10. *Revision after unplanned interim analysis:*[F] 165 patients required for 114 PFS events to provide 80% power to detect an HR=0.67 using a one-sided alpha=0.10. *Revision after second interim analysis:*[G] The number of required PFS events reduced to 95 to provide 75% power to detect an HR=0.67 or 98% power to detect HR=0.50, using a one-sided alpha=0.10 (stratified log-rank test)	84 vs. 81	Central IWRS, stratified[H] using block size of 6	No	No[I]	Yes	Yes[J]	No	Yes

Abbreviations:
HR - hazard ratio; ITT - intent-to-treat analysis; IRT - interactive randomization technology; IWT - interactive web-based randomization system; PFS - progression-free survival.

Notes:
[A] The sample size was determined based on the assumptions of 9 month median PFS in the placebo-letrozole group and 13 months in the palbociclib-letrozole group (a difference deemed clinically significant), a 15% drop-out rate, patient accrual over 15 months, and a follow-up period of 10 months.

[B] The efficacy stopping boundary for rejecting the null hypothesis (i.e., median PFS is the same in both groups) was p≤0.000013, with proper adjustment made to preserve the overall alpha of the trial (i.e., type-1 error rate). If an HR≥1 was observed at interim analysis the trial would be stopped for futility.
[C] Randomization was stratified by disease site, disease-free interval, and prior (neo)adjuvant hormonal therapy (yes/no).
[D] The Sponsor was blinded during interim efficacy analyses, but unblinded to final efficacy analyses.
[E] Several amendments were made to the statistical plan of PALOMA-1. The study was initially designed as a phase 1/2 trial. Phase 1 was intended to assess initial safety and efficacy data in a Cohort of ER-positive and HER2-negative patients (n=60, Cohort 1). Phase 2 was intended to assess the primary outcome of the study in a Cohort of patients with additional biomarkers including CCND1 amplification and/or p16 loss (n=150, Cohort 2). The required sample size was initially based on Cohort 2 only and based on the assumption that combination palbociclib + letrozole would increase PFS from 9 months to 13.5 months compared to letrozole alone.
[F] The Cohorts were subsequently combined when an unplanned interim analysis of Cohort 1 data (based on 31 progression events) showed twice as many patients in the control arm coming off study due to disease progression (HR=0.35, 95% CI, 0.17-0.72; p=0.006). Further patient enrolment was consequently stopped and the statistical plan was amended (prior to any efficacy analyses) to be based on the 165 patients already enrolled. The event rate assumption remained unchanged.
[G] After a second interim analysis (conducted when approximately half [61] of the expected events occurred), the number of events required for the final analysis of PFS was amended and reduced to 95. This change was made after noting a substantial fall in the event rate over time.
[H] Randomization was stratified for disease site, disease-free interval, and study Cohort.
[I] Outcome assessment was not performed using blinded central review. An independent blinded central review of PFS data was performed retrospectively after patient accrual was completed. Data analyses were also unblinded and performed by the sponsor; randomization codes were released at the time of interim and final data analyses.
[J] The final analysis applies to the primary outcome (investigator assessed PFS); survival data are considered immature as of the Nov. 29, 2013 data analysis.

a) Trials

The PALOMA trials were both international, multi-centred RCTs. PALOMA-1, which preceded PALOMA-2, was a phase 2 trial evaluating the initial efficacy and safety of palbociclib-letrozole compared to letrozole alone as first-line treatment in women with ER+, HER2- ABC. PALOMA-2, a placebo-controlled phase 3 trial, was designed to confirm the results of PALOMA-1 and determine whether palbociclib-letrozole was indeed superior to letrozole alone, in terms of prolonging progression-free survival (PFS), among post-menopausal women with ABC. The trials compared identical active interventions and schedules, assessed similar outcomes, and enrolled patients based on very similar eligibility criteria (refer to Table 4 for a complete list of criteria) that included the following:

- ≥18 years of age
- Locally recurrent or metastatic disease not amenable to surgery
- No prior treatment for ABC, including any previous treatment with a CDK inhibitor
- Specifically excluded patients with active brain metastases

Aside from trial phase, the main features that distinguished the trials included the following:

- PALOMA-2:
    - Included patients with an ECOG performance status of 0 to 2
    - Excluded patients who had disease recurrence while on or within 12 months of completing (neo)adjuvant treatment with letrozole or anastrozole
    - Included a placebo-control and double-blinding
    - Stratified randomization by prior hormone therapy, in addition to disease-site and disease-free interval
    - Assessed patient-reported quality of life (QOL) using validated instruments

- PALOMA-1:
    - Included patients with a ECOG performance status of 0 or 1
    - Excluded patients receiving letrozole as (neo)adjuvant treatment within 12 months of study entry
    - Open-label design
    - Assessed patient-reported pain severity and interference
    - Multiple data-driven trial protocol changes compromised the statistical plan of the trial raising concern about the internal validity of the trial and the magnitude of the treatment effect observed

PALOMA-2[1,2]

PALOMA-2 enrolled patients between February 2013 and July 2014 at 186 sites from 17 countries, including Canada (14 sites), Australia, Belgium, France, Germany, Hungary, Ireland, Italy, Japan, Korea, Poland, Russia, Spain, Taiwan, Ukraine, UK and the US.

Patients were randomized in a 2:1 ratio to the palbociclib-letrozole or placebo-letrozole treatment groups, respectively, using central randomization methods. The randomization procedure was stratified by disease site (visceral vs. non-

visceral),[a] disease-free interval from the end of (neo)adjuvant treatment to disease recurrence (≤12 months, >12 months, versus de novo metastatic disease), and prior hormonal therapy (yes/no). Disease status was assessed every 12 weeks (±7 days) from the date of randomization and was performed until documented disease progression (radiographically and/or clinically as per RECIST version 1.1), initiation of new anti-cancer therapy, or discontinuation of the patient from the trial. After discontinuing the treatment phase of the trial, patients were followed every six months from the last dose of study drug and assessed for overall survival (OS) and patient-reported QOL. The trial was double-blind, therefore patients and investigators were blinded to assigned treatment.

Pfizer funded the trial, however, limited information is known regarding the extent of the funder's role in the conduct of the trial (e.g., study design, treatment administration, data collection, database access) since the trial has yet to be published and peer-reviewed. Information contained in submission documents confirms that the funder oversaw conduct of the trial, and had an active role in data analysis and interpretation.

The primary outcome of the trial was investigator-assessed PFS, defined as the time from randomization to first documentation of progressive disease, or death due to any cause in the absence of documented progression. The secondary outcomes of the trial included the following:

- OS
- Objective response rate (ORR, complete and partial)
- Duration of response
- Disease control (defined as complete plus partial response plus stable disease ≥24 weeks)
- QOL measured using the Breast Functional Assessment of Cancer Therapy (FACT-B) and EuroIQoL five dimensions (EQ-5D) instruments
- Safety

In PALOMA-2, all efficacy analyses were performed using local investigator tumour assessments and analyzed based on intent-to-treat (ITT). A blinded independent central review (BICR) was prospectively planned but conducted retrospectively to verify tumour response and disease progression outcomes. The Kaplan Meier method was used to generate survival curves for all time-to-event outcomes including OS, PFS and duration of response. Differences in OS and PFS between treatment groups were analyzed using a log-rank test stratified by randomization variables. Hazard ratios (HR) and 95% confidence intervals (CIs) were generated using Cox proportional hazards models. For duration of response, all patients who had an objective response were included in analyses. Sponsor data analysts were blinded to treatment assignment during interim efficacy analyses but were unblinded to final efficacy analyses. Subgroup analyses were pre-specified and performed for stratification factors and baseline characteristics**.** The statistical analysis plan (SAP) prospectively planned for extensive sensitivity analyses to

[a] Visceral refers to any lung (including pleura) and/or liver involvement; and non-visceral refers to absence of lung (including pleura) and/or liver involvement.

investigate the robustness of the treatment effect estimate.[b] Refer to Table 5 for a more detailed summary of statistical and sample size considerations in the trial.

A total of seven protocol amendments took place over the trial. Upon review, the majority of amendments were editorial in nature or related to assessment schedules or procedural changes. There were two revisions to the SAP that involved, (1) changing the interim analysis efficacy boundary to ensure the trial would only be stopped if the primary PFS analysis results were both statistically and clinically significant, and (2) increasing the sample size (to maintain appropriate power) prior to interim analysis to account for a possible decrease in palbociclib exposure, as observed in previous clinical studies, with the concomitant use of proton pump inhibitors and administration of the drug in a fasted state (which were permitted prior to Amendment 2). Both changes appeared appropriate to maintain the integrity of the SAP of the trial.

PALOMA-1[3]

PALOMA-1 enrolled patients from 50 sites in 12 countries that included Canada, France, Germany, Hungary, Ireland, Italy, Russia, South Africa, South Korea, Spain, Ukraine, and the United States. Patient enrolment occurred between December 2009 and May 2012 and was conducted using a sequential Cohort design involving two Cohorts of patients. In Cohort 1, patients were enrolled based on ER+ and HER2- status alone (biomarker-unselected group), whereas in Cohort 2 patients were also required to have amplification of cyclin D1 (CCND1) and/or loss of p16 (biomarker-selected group).

Patients were randomized in a 1:1 ratio to treatment groups using central randomization methods. Randomization was stratified by disease site (i.e., visceral, bone only, or other) and disease-free interval (>12 months from the end of adjuvant treatment to recurrence vs.≤ 12 months from the end of adjuvant treatment to recurrence or de novo metastatic disease).

The primary outcome of the trial was investigator assessed PFS, defined as the time from randomization to radiological evidence of disease progression or death on study.

The secondary outcomes of interest included the following:

- OS
- ORR
- Clinical benefit (defined as the sum of complete plus partial responses and stable disease for 24 or more weeks)
- Duration of response
- Pain severity and pain interference as measured by the modified Brief Pain Inventory short-form (BPI-sf), and
- Safety

[b] Sensitivity analyses performed included: an unstratified analysis, excluding patients whose ER+ status was not confirmed centrally, analysis based on patients as treated, an analysis based on stratification as per case report form, an analysis including disease progression or death as events regardless of initiation of new anti-cancer therapy, forcing actual assessment times to planned assessment times, if progressive disease occurred after an indeterminate assessment the date of the indeterminate assessment was used, assigned patients discontinuing treatment due to systemic deterioration of health or an adverse event as an event, excluding patient with major protocol deviations of inclusion/exclusion criteria, excluding patients who took palbociclib under fasting conditions or who took proton pump inhibitors, and investigating influence of bone-only disease.

The trial protocol was amended eight times over the course of the trial. Three amendments involved major changes to the SAP, which occurred after examinations of the trial data. The trial was originally designed as a phase 1/2 trial, with the intent to use Cohort 1 as an exploratory analysis of efficacy and safety, while the primary analysis was intended for Cohort 2. The original sample size calculation (refer to Table 5) was therefore based on Cohort 2 only and planned for the accrual of 150 patients with one interim analysis scheduled for futility only. During the trial it was observed that in Cohort 1 twice as many patients in the control group were coming off study due to disease progression compared to the experimental group. An unplanned interim analysis was performed and showed superior efficacy with combined treatment that was deemed clinically meaningful. These results were interpreted to suggest that further patient selection based on biomarker status beyond ER/HER2 was unlikely to further patient outcome. As a result, further patient accrual to Cohort 2 was stopped, and the SAP was amended to analyze the primary endpoint in Cohorts 1 and 2 combined. The authors report that this amendment was made ahead of viewing any data from Cohort 2. A total of 165 patients had been randomized at the time patient enrolment was stopped (66 in Cohort 1 and 99 in Cohort 2). The same assumptions that were used in the original sample size calculation were maintained (Table 5), the futility analysis was removed, and two (possibly three) additional interim efficacy analyses were added.[4] After the second interim analysis was conducted, a substantial fall in event rates was observed and prompted another amendment. The number of events triggering the final analysis of the primary outcome was reduced from 114 to 95.

The final analysis of PFS was conducted according to ITT. A hierarchal gate-keeping procedure was used for hypothesis testing in order to control the type I error rate for multiple comparisons but these adjustments were only performed for the primary outcome. Progression-free survival curves were generated using the methods of Kaplan-Meier, and differences between treatment groups were assessed using a stratified log-rank test (stratified by disease-site, disease-free interval and by Cohort). Hazard ratios and 95% CIs were estimated using cox proportional hazard regression models, and subgroup analyses were pre-specified and performed for baseline stratification factors and prognostic variables using multivariate analysis.

Due to the number of data-driven amendment changes, and considering the open-label design and small sample size of the trial, the FDA requested the sponsor conduct a BICR of the PFS data.[4] The BICR was carried out retrospectively and considered a secondary outcome of the trial. Sensitivity analyses of the PFS data were pre-planned (for both investigator and BICR analyses).[c] The statistical methods used to compare differences between groups in the secondary outcomes of interest were not reported in the primary trial publication. The FDA Statistical Review Report stated that OS data were analyzed using log rank tests and ORR data were assessed using a Cochran Mantel Hanzel test.[4]

Pfizer Inc. funded all aspects of the PALOMA-1 trial, including study design, conduct, treatment administration, and data collection. A steering committee,

[c] Sensitivity analyses performed included: an un-stratified analysis, an analysis stratified by per case report form (CRF) data, including symptomatic deterioration as disease progression, including disease progression or death after 28 days of treatment discontinuation as disease progression, forcing actual assessment times to planned assessment times, an as-treated population analysis, and multivariate analysis stratified by Cohort.

consisting of both independent and Sponsor staff, oversaw conduct of the trial and had unrestricted access to the trial database (raw and final trial data), which was held by the Sponsor. They were also responsible for data analysis, interpretation, and final publication preparation. It was reported that randomization codes were released at the time of interim and final data analyses.

b) Populations

The baseline characteristics of patients in the PALOMA trials are summarized in Table 6. In general, the distributions of patient characteristics appeared similar in the PALOMA trials, with the exception of higher proportions of patients with non-visceral site of disease and prior receipt of hormonal therapy in PALOMA-2; and more patients in PALOMA-1 with a shorter disease-free interval (≤ 12 months) from completion of (neo)adjuvant therapy to recurrence, which is likely explained by the high percentage of patients with de novo disease in this trial.

PALOMA-2[1,2]

Of the 666 patients randomized in PALOMA-2, 444 patients were randomized to the palbociclib-letrozole treatment group and 222 were allocated to placebo-letrozole. The treatment groups were considered well balanced for baseline demographic and prognostic characteristics; however, there did appear to be a greater number of patients with poorer performance status allocated to the placebo-letrozole arm. The Submitter confirmed there was an imbalance in ECOG status between the treatment groups that was statistically significant (p=0.0082), however, they provided the results of sensitivity analyses showing the treatment effect was robust after adjustment for ECOG status and other baseline characteristics. The median age of patients was 62 years, with approximately 39% (n=262) of patients aged 65 or older. Most patients were white (77%), from European countries (46%), and had an ECOG performance status of 0 (54%). Canadian patients comprised approximately 11% (n=70) of the trial population. A majority of patients had stage IV disease (97%) and approximately a third of patients presented with de novo stage IV disease (37%). Site of disease was generally equally distributed for visceral (49%) and non-visceral spread (51%). Disease-free interval was ≤ 12 months in 22% of patients and >12 months in 41% of patients. More patients received hormonal therapy (56%) as (neo)adjuvant treatment for their primary diagnosis than chemotherapy (48%), with tamoxifen being the most commonly received hormonal therapy (46%).

PALOMA-1[3]

For the Combined Cohort, a total of 165 patients were randomly assigned (ITT population); 84 were randomized to palbociclib-letrozole and 81 to letrozole alone. The authors reported balance between treatment groups in baseline demographic and prognostic variables except for disease site, disease-free interval, and previous treatment. The imbalances in stratification variables (disease site and disease-free interval) are most likely attributable to incorrect stratification factors used at the time of randomization for a significant percentage of patients. At the conclusion of the trial the Sponsor found 13% (n=22) and 18% (n=29) of patients misclassified for disease-free interval and disease site, respectively.[4]

The median age of patients was 63 years, with almost all patients presenting with stage IV disease (98%). The majority of patients were white[5] (90%) and had an ECOG status of 0 (55%). Site of disease was categorized as visceral, bone only, or other in 48%, 18%, and 34% of patients, respectively. A large proportion of patients had not

received any prior systemic therapy, with 49% of patients presenting with de novo advanced disease. Among patients previously treated in the adjuvant setting, 43% had received chemotherapy and 33% had received hormone therapy. Of the patients treated with hormone therapy, 29% were treated with tamoxifen and 17% were treated with aromatase inhibitors (AIs). More patients in the palbociclib-letrozole group had a shorter disease-free interval (≤ 12 months) from completion of adjuvant therapy to recurrence compared to the letrozole group; however, the increased percentage of patients with de novo disease in the combined treatment arm likely accounts for some of this difference. Canadian patients comprised 3% (n=5) of the trial population.

c) Interventions

In both PALOMA trials, all patients received a continuous regimen of letrozole at a dose of 2.5 mg once daily. Patients allocated to the experimental treatment groups of each trial received palbociclib at a dose of 125 mg once a day for three weeks followed by one week off in a 28-day cycle. In PALOMA-2, placebo was administered once daily on the same schedule as palbociclib. Treatment was continued until disease progression, unacceptable toxicity, withdrawal of consent, or death. Dose modifications were permitted in both trials, with dose reduction guidelines outlined for management of specific toxicities as well as criteria for resuming treatment. In PALOMA-2, no dose reductions of letrozole were allowed; however, patients experiencing specific adverse events (AEs) could have their dose of letrozole interrupted or delayed. Crossover was not permitted in either trial.

PALOMA-2[2]

The median duration of treatment and the median relative-dose intensity of study drugs received by patients were reported for the individual drugs in each treatment group. In the palbociclib-letrozole treatment group, the median duration of treatment was 603 days for palbociclib and 617 days for letrozole. The median relative dose intensity for palbociclib and letrozole was 93% (116.25 mg/day) and 100% (2.5 mg/day), respectively. In the placebo-letrozole group, the median duration of treatment was 413 days for placebo and 420 days for letrozole, and the median relative dose intensity was 100% for both study drugs. Dose reductions, interruptions and cycle delays all occurred more frequently in the palbociclib-letrozole treatment group. The percentages of patients treated with palbociclib (versus % observed with placebo) with at least one dose reduction, interruption, or cycle delay were 36% (vs. 1%), 70% (vs. 42%), and 68% (vs. 27%), respectively. There were 53% of patients who had a dose interruption attributable to letrozole in the palbociclib-letrozole treatment group compared to 45% in the placebo-letrozole group.

PALOMA-1

Limited information on treatment exposure for patients receiving palbociclib was provided in the trial publication. The FDA Medical Review Report provided a more comprehensive summary of these data.[5] The median daily dose of palbociclib was 125 mg (range, 79.6 to 266.7 mg) with a median duration of treatment exposure of 420 days. The relative dose intensity in the palbociclib-letrozole group was reported to be 94%. Dose reductions and dose interruptions occurred in 40% and 57% of patients, respectively.

d) Patient Disposition

The disposition of patients in the PALOMA trials is provided in Table 7.

PALOMA-2[2]

In PALOMA-2, all randomized patients received allocated treatment. At the time of the primary data-analysis of PFS, just over half of patients in the palbociclib-letrozole group and three-quarters of patients in the placebo-letrozole group had discontinued study treatment. In both treatment groups disease progression or relapse was the primary reason for treatment discontinuation. Data on the post-progression treatment received by patients was not provided.

Aside from the percentage of protocol deviations that were related to treatment discontinuations, no data were provided to pCODR on the major protocol deviations that took place during the course of the trial. A request was made to the Submitter for more complete information. In response to this request, they provided data on the major protocol deviations that took place during the trial; the overall data are summarized in Table 7. A substantial number of deviations, considered clinically significant, took place with a higher proportion (approximately 20% higher) occurring in the palbociclib-letrozole treatment group. Deviations related to inclusion/exclusion criteria, the investigational product/treatment, randomization, procedures and tests, safety reporting, concomitant treatments, and informed consent. Informed consent deviations were high in both treatment groups and were primarily related to obtaining consent prior to required approvals (i.e., ethics board and Sponsor). The higher frequency of concomitant treatment and investigational product deviations in the palbociclib-letrozole group primarily related to the use of prohibited medications (e.g., antibiotics for infections, steroids, and proton-pump inhibitors) and failing to retreat according to specified parameters following dose interruption or cycle delay (likely due to the incidence of neutropenia). The impact of these deviations on the efficacy findings of the trial is unknown, as only the influence of deviations related to inclusion/exclusion criteria, and not more prevalent deviations, were assessed in sensitivity analyses.

PALOMA-1[3]

At the final data analysis, 76% of patients in the palbociclib-letrozole group and 85% in the letrozole group had discontinued treatment. In both groups the primary reason for discontinuation was disease progression. At the final data analysis of PFS, the percentage of patients still receiving treatment on study was 23% in the palbociclib-letrozole group and 10% in the letrozole group. The post-progression treatment received by patients was not reported.

The number of protocol deviations that took place over the course of the trial was not reported in the trial publication. However, the FDA Medical Review Report,[5] which is publically available, cites that a substantial number of protocol deviations occurred in the trial (93%, n=154), with a higher proportion of these in the palbociclib-letrozole group (99%, vs. 88%). These deviations were related to eligibility criteria, randomization, the investigational product (i.e., dosing or schedule errors), conduct of the study and study assessments. Notable deviations included multiple patients being stratified incorrectly at randomization, assessments performed outside of the allowed time window, and patients being newly treated after study entry (i.e., bisphosphonates, surgery).

Major deviations occurred much less frequently and were similar between groups (9.5% for the combination vs. 7.4% for letrozole alone). These deviations primarily

concerned failure to comply with inclusion/exclusion criteria. The FDA reviewed in detail the deviations occurring in each group and for some deviations carried out post-hoc sensitivity analyses. Results from these investigations indicated protocol deviations did not impact the overall efficacy results of the trial.[4,5]

Table 6: Baseline patient characteristics in the PALOMA-1 and PALOMA-2 trials.

Trials	PALOMA-2[1,2]		PALOMA-1[3]					
			Combined Cohort ITT analysis population (n=165)		Patient Cohort 1 (n=66)		Patient Cohort 2 (n=99)	
Treatment Groups	Palbociclib + letrozole	Placebo + letrozole	Palbociclib + letrozole	Letrozole alone	Palbociclib + letrozole	Letrozole alone	Palbociclib + letrozole	Letrozole alone
No. patients randomized	444	222	84	81	34	32	50	49
Baseline patient characteristics, n (%) unless otherwise specified:								
Median age, years (range)	62 (30-89)	61 (28-88)	63 (41-89)	64 (38-84)	66 (41-89)	64 (42-75)	62 (46-83)	63 (38-84)
ECOG status:								
0	257 (58)	102 (46)	46 (55)	45 (56)	23 (68)	20 (63)	23 (46)	25 (51)
1	178 (40)	117 (53)	38 (45)	36 (44)	11 (32)	12 (38)	27 (54)	24 (49)
2	9 (2)	3 (1)	NA	NA	NA	NA	NA	NA
Disease stage:								
III	11 (3)	6 (3)	2 (2)	1 (1)	2 (6)	0	0	1 (2)
IV	433 (98)	216 (97)	82 (98)	80 (99)	32 (94)	32 (100)	50 (100)	48 (98)
Disease site:*								
Visceral	214 (48)	110 (50)	37 (44)	43 (53)	10 (29)	11 (34)	27 (54)	32 (65)
Bone	NR	NR	17 (20)	12 (15)	7 (21)	6 (19)	10 (20)	6 (12)
Other (non-visceral)	230 (52)	112 (51)	30 (36)	26 (32)	17 (50)	15 (47)	13 (26)	11 (23)
Disease-free interval:*								
>12 months from (neo) adjuvant treatment to recurrence	178 (40)	93 (42)	25 (30)	30 (37)	10 (29)	10 (31)	15 (30)	20 (41)
≤ 12 months from (neo) adjuvant treatment to recurrence (or de-novo advanced disease**)	99 (22)	48 (22)	59 (70)	51 (63)	24 (71)	22 (69)	35 (70)	29 (59)
De novo advanced disease only	167 (38)	81 (37)	44 (52)	37 (46)	19 (56)	17 (53)	25 (50)	20 (41)
Previous systemic therapy:								
None	NR	NR	44 (52)	37 (46)	19 (56)	17 (53)	25 (50)	20 (41)
Chemotherapy	213 (48)	109 (49)	34 (40)	37 (46)	11 (32)	14 (44)	23 (46)	23 (47)
Hormonal:	249 (56)	126 (57)	27 (32)	28 (35)	11 (32)	11 (34)	16 (32)	17 (35)
Tamoxifen	209 (84)	98 (78)	24 (29)	24 (30)	8 (24)	8 (25)	16 (32)	16 (33)
Anastrozole	56 (23)	29 (23)	8 (10)	11 (14)	4 (12)	5 (16)	4 (8)	6 (12)
Letrozole	36 (15)	16 (13)	2 (2)	1 (1)	0	0	2 (4)	1 (2)

Exemestane	30 (12)	13 (10.3)	4 (5)	2 (2)	3 (9)	1 (3)	1 (2)	1 (2)
Most recent hormonal therapy:								
Aromatase inhibitor	91 (37)	44 (35)	NR	NR	NR	NR	NR	NR
Antiestrogens	154 (62)	75 (60)	NR	NR	NR	NR	NR	NR
Other	4 (2)	7 (6)	NR	NR	NR	NR	NR	NR
Abbreviations: ECOG - Easter Cooperative Oncology Group; ITT - intent-to-treat; NA - not applicable; No./n - number; NR - not reported.								
Notes: *Based on case report form data. **Inclusion of denovo disease within ≤ 12 months disease interval applies to PALOMA-1 only.								

Table 7: Patient disposition in the PALOMA-1 and PALOMA-2 trials.

Trials	PALOMA-2[1,2]		PALOMA-1[3]					
			Combined Cohorts (n=165)		Cohort 1 (n=66)		Cohort 2 (n=99)	
Treatment arms, n (%)	Palbociclib + letrozole	Placebo + Letrozole	Palbociclib + letrozole	Letrozole alone	Palbociclib + letrozole	Letrozole alone	Palbociclib + letrozole	Letrozole alone
Patients randomized	**444**	**222**	**84**	**81**	**34**	**32**	**50**	**49**
Received allocated treatment	444 (100)	222 (100)	83 (99)	77 (95)	33 (97)	29 (91)	50 (100)	48 (98)
Did not receive allocated treatment	0	0	1 (1)	4 (5)	1 (3)	3 (9)	0	1 (2)
Withdrew consent	NR	NR	1 (1)	4 (5)	1 (3)	3 (9)	0	1 (2)
Patients continuing randomized treatment	199 (45)	61 (28)	19 (23)*	8 (10)*	NR	NR	NR	NR
Patients discontinuing randomized treatment	245 (55)	161 (73)	64 (76)	69 (85)	26 (76)	28 (88)	38 (76)	41 (84)
Primary reasons for discontinuation:								
Adverse events	33 (7)	10 (5)	11 (13)	2 (2)	8 (24)	1 (3)	3 (6)	1 (2)
Objective progression or relapse	171 (39)	126 (57)	42 (50)	57 (70)	16 (47)	22 (69)	26 (52)	35 (71)
Deterioration of health status	14 (3)	9 (4)	5 (6)	3 (4)	0	1 (3)	5 (10)	2 (4)
Death	6 (1)	2 (<1)	1 (1)	0	0	0	1 (2)	0
Withdrew consent	9 (2)	9 (4)	5 (6)	5 (6)	2 (6)	2 (6)	3 (6)	3 (6)
Protocol violation	4 (<1)	2 (<1)	NR	NR	NR	NR	NR	NR
Lost to follow-up	1 (<1)	0	NR	NR	NR	NR	NR	NR
Study terminated by Sponsor	1 (<1)	0	NR	NR	NR	NR	NR	NR
Other	6 (1)	3 (1)	0	2 (2)	0	2 (6)	0	0
Protocol deviations:								
Any deviation**	NR	NR	83 (99)	71 (88)	33 (97)	28 (88)	50 (100)	43 (88)
Major deviation***	479 (108)	198 (89)	8 (10)	6 (7)	1 (3)	3 (9)	7 (14)	3 (6)

Abbreviations: ITT - intent-to-treat; No./n - number; NR - not reported.

Notes:

* As reported in the text of the primary trial publication (p.31); in Figure 1 (p.27) it is reported that the number of patients continuing randomized treatment in the palbociclib-letrozole arm is 24% (n=20).

**Includes deviations related to: inclusion/exclusion criteria, investigational product (dose or schedule errors), concomitant medications, laboratory, visit schedule, procedure/tests, randomization, safety reporting, protocol-specific discontinuation criteria and other.[5]

*** Includes any significant deviation related to: inclusion/exclusion criteria, investigational product, procedure/tests, randomization, concomitant treatment, safety reporting, and informed consent.[5]

e) Limitations/Sources of Bias

Refer to Table 5 for a summary of key quality-related features of the PALOMA trials.

PALOMA-2

The quality of the PALOMA-2 trial was challenging to appraise in the absence of a peer-reviewed trial publication. The appraisal that follows is based on a single abstract[1] and data provided by the Submitter,[2] which are sources of evidence that fall short of providing a comprehensive account of all aspects of trial conduct. Therefore, additional limitations may come to light upon full publication of the trial.

Overall, the trial was well conducted owing to specific design features, including a placebo control, double-blind method, the use of appropriate randomization procedures, clear explanation of sample size considerations and the disposition of patients through the trial, prospectively planning a retrospective BICR of the primary endpoint (PFS), and performing all efficacy analyses by assigned treatment. These features address some of the design shortcomings of the PALOMA-1 trial.[3] However, the following limitations were noted:

- The very large number of major protocol deviations that occurred during the trial is a concern. These deviations were omitted from submission documents and were only presented when requested by pCODR. Further, their impact (considered major by the Submitter) on the results obtained was only investigated for one type of deviation, namely inclusion/exclusion criteria, which happened to be the least frequently occurring in the trial. The impact of more prevalent deviations (e.g., prohibited concomitant medications, investigational product/treatment) should have been assessed in sensitivity analyses and fully disclosed/presented in order to fully assess their influence on the trial results and understand why so many major deviations occurred in the trial.
- The assessment of QOL should be interpreted with caution as the number of patients who contributed to assessments substantially declined over the course of the trial. At some time points the percentages of patients included in analyses were less than 1%, which raises uncertainty about the reliability of the QOL findings. Further, the QOL analysis was also not adjusted for multiple comparison testing.
- Selective reporting is an obvious limitation to the PALOMA-2 data presented in this report as the trial has yet to be published in the public domain and undergo peer-review.

PALOMA-1

Overall, the PALOMA-1 trial[3] suffered from multiple flaws in design and execution, raising concerns about both the internal and external validity of the trial results, and thus uncertainty around the true magnitude of PFS benefit observed with palbociclib-letrozole. Specifically,

- Many of the problematic issues relate to the fact that the trial was not originally designed with the intent of being a registration trial for regulatory approval. This partially explains why more rigorous methods of trial conduct (e.g., prospective BICR of outcome data and data analysis, conventional two-sided significance testing) were not done and why the sample size is too small

to reliably determine the true effect size associated with palbociclib-combined treatment.

- The open-label design, especially without a prospective independent and blinded assessment of outcome and data analysis, puts the trial at risk of a number of different biases that can affect internal validity. The retrospective BICR of PFS data that was performed cannot eliminate all potential biases since treatment decisions were in fact not based on the scanned images used in the BICR. The impact of bias is evident (but not limited to) in the post-hoc analysis that showed investigator bias was likely in the determination of stable disease versus progressive disease status in the experimental arm.
- In total, there were eight amendments made to the trial protocol; three of which were data driven, and included changes to the SAP. These changes compromised the SAP of the trial and thus cast doubt on the integrity and magnitude of the reported treatment effect estimates, make associated p-values difficult to interpret, and preclude making statistical inferences from the trial data.[4] Further, all these changes raise the question of how many times the trial Sponsor actually looked at the data since Sponsor staff were involved at all levels of trial conduct and the database was held by the Sponsor.
- There were a very large number of protocol deviations (93.3%). These included deviations related to inclusion/exclusion criteria, randomization (i.e., incorrect stratification of patients), study conduct (including study assessments performed outside window period), and patients inappropriately started on treatments after trial entry. While sensitivity and post-hoc analyses confirmed the robustness of the trial results to these deviations, these analyses are still retrospective in nature and cannot completely rule out the influence of trial conduct errors on the results obtained.
- The trial did not assess QOL but did include an assessment of patient-reported pain including pain severity and pain interference with daily activities. The results of these analyses are limited and difficult to interpret due to the open-label design of the trial and failure to adjust for multiple comparisons and the concomitant use of pain medications.
- The Submitter commented on the pCODR Expert Review Committee's (pERC's) Initial Recommendation on the original submission that the significance level for the efficacy analyses in the efficacy summary was not α=0.05 but a much more stringent one-sided a=0.025, which was equivalent to a two-sided α=0.05. It is unclear what efficacy summary the Submitter is referring to as the main trial publication[3] states that the trial was designed using a one-sided α=0.10 and it also summarizes the multiple unplanned data-driven changes that were made to the SAP. Furthermore, it states that the significance level for the final analysis was adjusted for the multiple analyses; however, there is no reporting of the use of a more stringent one-sided α=0.025 for the final analysis. From a statistical point of view, it can be argued that the reported p-values are not meaningful anyway considering the SAP of the trial was compromised, which precludes making any statistical inferences from the trial data. The Methods Team evaluation is in line with the FDA's statistical review and evaluation,[4] which raised similar statistical concerns with the trial.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

A summary of the key efficacy results from the PALOMA trials can be found in Table 8.

Primary Outcome

Investigator-Assessed Progression-free Survival

In both PALOMA trials, PFS by investigator assessment was significantly prolonged in patients treated with palbociclib-letrozole compared to letrozole alone, after approximately two years of follow-up. The PFS benefit associated with palbociclib-letrozole was in the range of 10 months (over letrozole alone) in both trials, and was consistently demonstrated in almost all patient subgroups examined. The results of BICR analyses of PFS, conducted in both trials, confirmed the median PFS benefit but estimated the magnitude of overall benefit to be lower than the investigator assessment.

PALOMA-2[1,2]

The cut-off date for the final efficacy analysis of PFS was February 26, 2016, at which point median follow-up time was approximately 23 months. At this time, a total of 331 PFS events had occurred, 194 (43.7%) in the palbociclib-letrozole group and 137 (61.7%) in the placebo-letrozole group. Median PFS time was significantly longer in the palbociclib-letrozole group at 24.8 months compared to 14.5 months in the placebo-letrozole group, a difference in PFS that was statistically significant (HR=0.58, 95% CI, 0.46 to 0.72; one-sided p-value<0.000001).

The PFS benefit associated with palbociclib-letrozole was consistent in all pre-specified patient subgroups (based on randomization factors and baseline characteristics) examined (all HRs <1, and 95% CI excluded the value of 1), with the exception of the subgroup of patients with two disease sites (HR=0.68, 95% CI, 0.42 to 1.10).

PALOMA-1[3]

The data cut-off date for the final analysis of PFS was November 29, 2013. Median follow-up times for the palbociclib-letrozole and letrozole alone treatment groups were 29.6 months and 27.9 months, respectively. At the time of data cut-off, 41 PFS events had occurred in the combined treatment group compared to 59 in the letrozole alone group. Median PFS time was statistically significantly longer in patients receiving combined treatment compared to letrozole alone (20.2 months versus 10.2 months; HR=0.49, 95% CI, 0.32 to 0.75; one-sided p-value=0.0004). The treatment effect was also observed within each Cohort; however, it was of less magnitude in Cohort 2, the biomarker-selected population (Table 8).

The PFS benefit associated with palbociclib-letrozole was consistent across all baseline stratification factors and prognostic variables examined (all confidence intervals excluded the value of 1) with the exception of the subgroup of patients who had disease recurrence within ≤12 months of the end of adjuvant therapy (excluding patients with de novo disease presentation). It should be noted that this subgroup was one of the smallest patient subgroups analyzed (n=29).

The planned sensitivity analyses of PFS data were reported to be consistent with the primary analysis. The data supporting these analyses were provided in the FDA Medical Review Report and showed HRs ranging from 0.41 to 0.49 with most p-values <0.0001.[5]

Key Secondary Outcomes

Blinded Independent Central Review (BICR) of Progression-free Survival

PALOMA-2[2]

The radiographic images of all randomized patients were included in the BICR. The result of the BICR analysis was consistent with the investigator assessment; however, the BICR analysis obtained a treatment estimate of slightly lower magnitude (HR=0.65, 95% CI, 0.51 to 0.84; one-sided p-value=0.0005). The median PFS times were 30.5 months for the palbociclib-letrozole group and 19.3 months for the placebo-letrozole group (Table 8). An analysis was performed to assess the discordance (palbociclib-letrozole versus placebo-letrozole) between the investigator assessment and the BICR analysis; it determined that the early [-4.1% (36.1% versus 40.1%) and late discordance rates [5.4% (50.4% versus 45%)] suggested no bias in the investigator assessment analysis favouring the experimental treatment group. The threshold or cut-off point used to identify bias, however, was not indicated. The overall discordance rate between the two analyses was -13.3% (31.8% versus 45%).

PALOMA-1

The results of the BICR analysis of PFS data were not included as part of the primary trial publication but were reported as part of the FDA Medical Review Report.[5] The Sponsor obtained the data for this analysis, which involved retrospectively collecting patients' radiographic images and submitting them to a third party for BICR. Retrospective data were available for 161 of the 165 randomized patients who comprise the combined Cohort ITT analysis population.

For the Combined Cohort, the results of the BICR analysis confirm the investigator assessment with palbociclib-letrozole associated with an improvement in median PFS of approximately 10 months over letrozole alone (Table 8). The result obtained, however, is of lower magnitude (HR=0.62, 95% CI, 0.38 to 1.02, p=0.03 than that observed with the investigator assessment. For the individual Cohort results, refer to Table 8.

The pre-planned sensitivity analyses performed for the BICR analysis showed treatment effects that favoured combined treatment; however, they were all of lower magnitude (HRs ranged from 0.62 to 0.70 with no p-values <0.01) compared to the investigator-assessed sensitivity analyses.

The differences in PFS analysis results between the investigator assessment and the BICR assessment were explored through multiple post-hoc exploratory analyses. These analyses showed that differences in censoring rates could partially explain the differences. Investigator bias was also a plausible cause since there was an imbalance between investigator assessment of stable disease and BICR assessment of progression events in the combination group compared to the letrozole group (i.e., cases where the investigator assessment determined stable disease in the palbociclib-letrozole group while the BICR analysis determined disease progression).

The FDA concluded that although post-hoc analyses are exploratory and thus cannot be used to infer statistical significance, they aligned with original primary analysis results and the pre-planned sensitivity analyses (by either investigator or BICR assessment) showing longer PFS with palbociclib-letrozole compared to letrozole alone. The true magnitude of PFS benefit, however, was indicated to be uncertain owing to the many issues associated with the trial.

Objective Response Rate

PALOMA-2[1,2]

The overall ORR (the sum of complete and partial responses) for all randomized patients (with or without measurable disease) was higher in the palbociclib-letrozole group (42.1 versus 34.7; odds ratio=1.40, 95% CI, 0.98 to 2.01; p=0.03). When only patients with measurable disease at baseline were considered (n=509; 338 patients in the palbociclib-letrozole group and 171 in the placebo-letrozole group), the difference in ORR between the treatment groups was even higher in favour of palbociclib-combined treatment (55.3% versus 44.4%; odds ratio=1.55, 95% CI, 1.05 to 2.28; p=0.01). A majority of partial versus complete responses contributed to the ORR in both treatment groups (Table 8).

PALOMA-1[3]

The overall ORR favoured palbociclib-letrozole compared to letrozole alone (43% vs. 33%) but the difference did not reach statistical significance (p=0.13). Response rates were driven by partial responses with only one complete response observed in each treatment group. A similar ORR result was observed among patients with measurable disease (55% versus 39%, p=0.047; n=131).

Duration of Response

PALOMA-2[2]

Among patients with measurable disease at baseline (n=509), duration of response (complete and partial responses) per investigator assessment was longer for patients in the palbociclib-letrozole group at 22.5 months compared to 16.8 months in the placebo-letrozole group. No statistical comparison of these data was performed.

PALOMA-1[3]

Duration of response was much longer among patients in the palbociclib-letrozole group. Median duration of response was 20.3 months for the combined treatment group compared to 11.1 months in the letrozole alone group. A statistical comparison of these data was not reported.

Clinical Benefit

PALOMA-2[1,2]

The clinical benefit response rate (disease control), defined as the sum of complete plus partial responses and stable disease for a period of ≥ 24 weeks, which included patients with or without measurable disease at baseline, was achieved in a higher percentage of patients in the palbociclib-letrozole treatment group compared to the placebo-letrozole group (84.9% versus 70.3%; odds ratio=2.39, 95% CI, 1.58 to 3.59; p<0.0001).

PALOMA-1[3]

Clinical benefit was achieved in a significantly greater proportion of patients in the palbociclib-letrozole group (81%) compared to the letrozole alone group (58%); this difference was statistically significant (p=0.0009).

Overall Survival

PALOMA-2[1,2]

An interim analysis of OS was performed at the time of the primary PFS analysis, which was based on 133 deaths (95 in the palbociclib-letrozole group and 38 in the placebo-letrozole group) and represents 34% of the required 390 deaths for the final assessment of OS. This analysis did not meet the pre-specified level for statistical significance and therefore OS data were deemed immature and will not be reported until the required number of deaths has been observed.

PALOMA-1[3]

At the time of the final analysis of PFS data, OS data were deemed immature. At that time, 30 deaths had occurred in the palbociclib-letrozole group and 31 had occurred in the letrozole alone group; median OS estimates were 37.5 months and 33.3 months, respectively. The trial was not powered to detect differences in OS between groups. After a median follow-up of approximately 29 months, the data favoured combined treatment but no statistically significant difference in OS between groups was observed (HR=0.81, 95% CI, 0.49 to 1.35; two-sided p=0.42).

Table 8: Efficacy Outcomes in the PALOMA-1 and PALOMA-2 trials.

Trials	PALOMA-2[1,2]		PALOMA-1[3]	
Treatment Groups	Palbociclib + Letrozole	Placebo + Letrozole	Palbociclib + Letrozole	Letrozole alone
Median follow-up, months	23	22.3	29.6	27.9
No. patients remaining on treatment, n (%)	199 (45)	61 (28)	19 (23)	8 (10)
Primary Outcome - Investigator Assessed PFS[A]				
			Combined Cohorts (ITT population)	
n	n=444	N=222	n=84	n=81
No. PFS events (%)	194 (43.7)	137 (61.7)	41(48.8)	59 (72.8)
Median PFS, months (95% CI)	24.8 (22.1 to NE)	14.5 (12.9 to 17.1)	20.2 (13.8 to 27.5)	10.2 (5.7 to 12.6)
Hazard ratio (95% CI; one-sided p-value)	0.58 (0.46 to 0.72; p<0-000001)		0.49 (0.32 to 0.75; p=0.0004)	
			Cohort 1	
n			n=34	n=32
No. PFS events (%)			15 (44.1)[E]	25 (78.1)[E]
Median, months (95% CI)			26.1 (11.2 to NR)	5.7 (2.6 to 10.5)
Hazard ratio (95% CI; one-sided p-value)			0.30 (0.16 to 0.57; p<0.0001)	
			Cohort 2	
n			n=50	n=49
No. PFS events (%)			26 (52)[E]	34 (69.4)[E]
Median, months (95% CI)			18.1 (13.1 to 27.5)	11.1 (7.1 to 16.4)
Hazard ratio (95% CI; one-sided p-value)			0.51 (0.30 to 0.85; p=0.0046)	
Secondary Outcome - BICR-assessed PFS[A,E]				
			Combined Cohorts (ITT population)	
n	n=444	n=222	n=84	n=81
No. PFS events (%)	152 (34.2)	96 (43.2)	31(36.9)	33 (40.7)
Median PFS, months (95% CI)	30.5 (27.4 to NE)	19.3 (16.4 to 30.6)	25.7 (17.7 to NR)	14.8 (9.3 to 20.4)
Hazard ratio (95% CI; one-sided p-value)	0.65 (0.51 to 0.84; p=0.0005)		0.62 (0.38 to 1.02; p=0.02)	
			Cohort 1	
n			n=34	n=32
No. PFS events (%)			11 (32.4%)	9 (28.1%)
Median, months (95% CI)			31.6 (11.2 to NR)	38.6 (7.5 to 38.6)
Hazard ratio (95% CI; one-sided p-value)			0.73 (0.30 to 1.78; p=0.24)	
			Cohort 2	
n			n=50	n=49
No. of PFS events (%)			20 (40)	24 (49)
Median, months (95% CI)			20.3 (12.2 to NR)	14.6 (8.1 to 20.0)
Hazard ratio (95% CI; one-sided p-value)			0.58 (0.32 to 1.05; p=0.03)	
Other Key Secondary Outcomes				
			Combined Cohorts (ITT population)	
n	n=444	n=222	n=84	n=81

Objective Response Rate[B] % (95% CI)	42.1 (37.5 to 46.9)	34.7[F] (28.4 to 41.3)	43(32-54)	33 (23-45)
One-sided p-value	p=0.03		p=0.13	
Complete response	10 (2)	5 (2)	1 (1)	1 (1)
Partial response	196 (44)	80 (36)	35 (42)	26 (32)
Stable disease	191 (43)	88 (40)	37 (44)	30 (37)
≥ 24 months	NR	NR	32 (38)	20 (25)
< 24 months	NR	NR	5 (6)	10 (12)
Progressive disease	NR	NR	3 (4)	18 (22)
Indeterminate	NR	NR	8 (10)	6 (7)
Duration of Response[C]				
Median duration in months (95% CI)	22.5 (19.8 to 28)	16.8 (15.4 to 28.5)[F]	20.3 (13.4 to 25.8)	11.1 (9.3 to 31.6)
p-value	NR		NR	
Clinical Benefit/Disease Control[D]				
No. (%) patients achieving clinical benefit	NR (84.9)	NR (70.3)	68 (81)	47 (58)
One-sided p-value	p<0.0001		p=0.0009	
Overall Survival				
No. deaths	95	38	30	31
Median, months (95% CI)	NA	NA	37.5 (28.4 to NE)	33.3 (26.4 to NE)
Hazard ratio (95% CI; two-sided p-value)	NA		0.81 (0.49 to 1.35; p=0.42)	

Abbreviations: BICR - blinded independent central review; CI - confidence interval; ITT - intent-to-treat; No./n = number; NA - not available; NE - not estimable; NR - not reached; PFS - progression-free survival.

Notes:
[A] Defined at the time from randomization to radiological disease progression or death on study.
[B] Defined as the sum of complete plus partial responses.
[C] Duration of complete or partial response.
[D] Defined as the sum of complete plus partial responses and stable disease for 24 weeks or more.
[E] Source: FDA Medical Review Report.[5]
[F] Includes one patient with bone only disease at baseline; all other patients had measurable disease at baseline.

Patient-reported Health-related Quality of Life and Health Status

The patient-reported outcomes (PRO) assessed in the PALOMA trials included health-related QOL in PALOMA-2 using FACT-B and EQ-5D instruments, and pain in PALOMA-1, which included an assessment of pain severity and its interference with daily activities, measured using the mBPI-sf.

PALOMA-2[2]

The FACT instrument assesses patients QOL using a set of 27 questions (FACT-G) divided into four subscales [physical well-being (PWB), social/family well-being (SFWB), emotional well-being (EWB), and functional well-being (FWB)]. The FACT-G is the sum of the scores from the 27 questions. The FACT-B instrument comprises the FACT-G and a breast-specific module (BSC), which is a 10-item module that measures patient concerns related to breast cancer (comprising 37 items altogether). Patients respond on a likert scale where 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much.

The EQ-5D is a six-item instrument that assesses health status in terms of a single-index value or utility score. It consists of five current health states (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The patient rates each state on a three-level scale (1=no problem, 2=some problem, and 3=extreme problem) with higher levels indicative of greater severity of impairment. The instrument also includes a visual analogue scale (VAS), which records the patients' self-rated health on a scale from 1 (worst imaginable health state) to 100 (best imaginable health state). Published weights are available that allow for creation of a single summary score, which ranges from 0 to 1, with low scores representing a higher level of dysfunction and 1 equating to perfect health.

FACT-B and EQ-5D Assessment

Patients completed both instruments pre-dose on day 1 of cycle 1 through cycle 3, then on day 1 of every other subsequent cycle starting with cycle 5 and then at the end of study treatment. After discontinuation from the active treatment phase of the trial, FACT-B questionnaires continued to be collected every 6 months from the last dose of study treatment until permanent discontinuation from the trial, or end of follow-up, which ever occurred first.

Analyses of PRO outcome data were carried out on patients comprising the ITT population who had completed a baseline assessment and at least one post-baseline assessment prior to study discontinuation. The following PRO scores were assessed in the trial: FACT-G total score, FACT-G subscales, BCS, FACT-B total score, trial outcome index (TOI)[d], EQ-5D index, EQ-VAS, and time-to-deterioration (TTD). Both total scores and change from baseline were compared between treatment groups at various time points using a repeated measures mixed effects model analysis adjusted for covariates (i.e., variables of treatment, time, treatment by time, and baseline). No adjustments were made for multiple comparisons. Time-to-deterioration, defined as the time between baseline and the first occurrence of an increase of ≥7 points in FACT-B scores, was assessed using the methods of Kaplan Meier and log-rank tests to compare treatment groups, and defined as a decrease of 7 points based on the minimally important difference (MID) for the FACT-B score. The MID for instrument total scores and subscales are provided in Table 9.

Results

For each PRO, the percentage of patients completing questionnaires substantially declined over the course of active treatment (ranged from 99% at baseline to <1% at cycle 37), with increases in compliance at the end of treatment (in the range of 40% to 60%). The substantial decline in compliance over time in both treatment groups should be considered when interpreting the results.

No statistically significant differences were observed between the palbociclib-letrozole versus the placebo-letrozole treatment groups in overall mean total scores (FACT-B: 103.4 vs. 103.7, p=0.7822; FACT-G: 78.8 versus 78.7; p=0.8825; EQ-5D: 0.74 versus 0.71; p=0.0925) or for any subscales (FACT-B BCS: 24.5 versus 25.2, p=0.0552; FACT-G PWB: 21.8 versus 22.1, p=0.4144; FACT-G SFWB: 21.5 versus

[d] The TOI score is the sum of FACT-G subscales (physical well-being and functional well-being) and BCS, comprising 24 items, and analyzed the same as the FACT-G with a MID of 5-6 points.

21.4, p=0.7617; FACT-G EWB: 17.2 versus 17.0, p=0.5381; FACT-G FWB: 18.3 versus 18.4, p=0.7074).

Overall mean changes from baseline for PRO scores are summarized in Table 9. Positive mean scores are indicative of an improvement from baseline and negative mean scores indicate a deterioration from baseline. Although deterioration was observed over time for some PRO in both treatment groups compared to baseline scores, the degree of deterioration did not reach the MID for any PRO, and there were no statistically significant differences in overall change from baseline scores between the treatment groups for any of the PRO total scores (FACT-G, FACT-B, EQ-5D including VAS) or subscales examined (BCS, and FACT-G PWB, SFWB, EWB, FWB). There was also no statistically significant difference in TTD in FACT-B total scores between the palbociclib-letrozole and placebo-letrozole treatment groups (HR=1.04, 95% CI, 0.84 to 1.30; p=0.663).

PALOMA-1[6,9]

Modified Brief Pain Inventory (mBPI-sf)

The mBPI-sf instrument is validated and commonly used in clinical trials including cancer patients. In brief, the inventory includes 13 questions that make up two scales and two single items. Four questions comprise the pain severity scale (i.e., relate to worst pain, least pain, average pain, and pain right now) and seven comprise the pain interference scale (relate to general activity, mood, walking, work, relations with others, sleep and enjoyment of life). Each question is based on an 11-point numerical rating scale ranging from 0 (no pain or does not interfere) to 10 (pain as bad as you can imagine or completely interferes). The two single items of the inventory, which address percentage of pain relief provided by medication and the presence of pain other than everyday kinds of pain, were not included as part of the assessment.

The primary trial publication did not report results for this outcome; however, results were published in a second publication.[9] The trial record for PALOMA-1 on the clinicaltrials.gov website also provides additional summary data for the Combined and individual Cohorts.[6] The results are provided in Table 10. To be included in the analysis, patients had to have had at least one dose of study treatment, baseline data, and at least one post-baseline measurement. 150 patients (76 in the palbociclib-letrozole group and 74 in the letrozole alone group) were included in analyses. It was reported that most patients (>95%) had a score for each pain scale at each treatment cycle.[9] Mean changes from baseline (on both scales) to the end of treatment (approximately 41 months) were compared using two-sided t-tests. The mean difference between arms that was considered clinically meaningful was not reported.

The majority of patients in both treatment groups had either mild or no pain at baseline; specifically, 83% of patients in the palbociclib-letrozole group and 73% of patients in the letrozole group had a pain severity scale score of ≤ 3, respectively; while 71% and 76%, respectively, had pain interference scale scores of ≤ 3.[9] Further, no differences in mean baseline scores were observed in either pain scale between treatment groups at baseline.

The results of both analyses generally show no significant differences in either pain severity or pain interference from baseline to end of treatment between groups. At earlier treatment cycles, which included more patients, the palbociclib–letrozole group showed greater numeric reductions from baseline compared to the letrozole alone group for pain severity (statistically significant at cycles 5, 6, 7, 8, 10 and 12;

p<0.05) and pain interference (not statistically significant at any cycle). These analyses included 43 cycles of treatment and were not adjusted for multiple comparisons or for the concomitant use of medications to control pain.[9] Overall, the addition of palbociclib to letrozole did not appear to affect pain outcomes, in either direction, as measured by the mBPI-sf.

Table 9: Patient-reported outcomes of health-related quality of life and health status assessed in the PALOMA-2 trial.[2]

Scale	MID	Palbociclib + letrozole (n=439)		Placebo + Letrozole (n=218)		Change from Baseline Mean Difference[F]		p-value
		Mean Change from Baseline	95% CI	Mean Change from Baseline	95% CI	Mean	95% CI	
FACT-G Total Score[A]	5-6 points	-0.390	-1.46 to 0.68	-0.532	-2.08 to 1.02	0.142	-1.74 to 2.03	0.8825
Physical well-being	2-3 points	-0.500	-0.90 to -0.20	-0.3	-0.80 to 0.30	-0.3	-0.90 to 0.40	0.4144
Social/Family well-being		-0.6	-1.00 to -0.20	-0.7	-1.20 to -0.10	0.1	-0.60 to 0.80	0.7617
Emotional well-being		0.7	0.40 to 1.00	0.5	-0.10 to 0.90	0.2	-0.40 to 0.70	0.5381
Functional well-being		0.2	-0.20 to 0.60	0.3	-0.30 to 0.90	-0.1	-0.80 to 0.60	0.7074
BSC[B]	2-3 points	0.189	-0.18 to 0.56	0.829	0.29 to 1.37	-0.639	-1.29 to 0.01	0.0552
TOI Score[C]	5-6 points	0.014	0.00 to 0.03	-0.010	-0.03 to 0.01	-0.8016	-2.40 to 0.79	0.0925
FACT-B Total Score[D]	7-8 points	-0.106	-1.42 to 1.21	1.196	-0.32 to 2.71	-0.325	-2.63 to 1.98	0.7822
EQ-5D[E]	0.06	0.014	0.00 to 0.03	-0.010	-0.03 to 0.01	0.023	-0.004 to 0.051	0.0925

Abbreviations: BSC - breast cancer subscale; CI - confidence interval; EQ-5D - EuroQol 5-Dimensions; FACT-B - Functional Assessment of Cancer Therapy Breast Specific Module; FACT-G - Functional Assessment of Cancer Therapy - General; MID - minimally important difference; TOI - Trial Outcome Index.

Notes:
[A] FACT-G total score is the sum of physical well-being, social/family well-being, emotional well-being, and functional well-being;
[B] BSC based on patients who completed >50% of the questions for this subscale.
[C] TOI score is the sum of physical well-being, functional well-being, and BSC.
[D] FACT-B total score is the sum of FACT-G subscales (physical well-being, social/family well-being, emotional well-being, functional well-being) and BSC; based on patients who completed >80% of questions and have valid scores for subscales.
[E] EQ-5D based on patients who completed all 5 items needed to calculate index-based summary score at respective cycle.
[F] Change from baseline between treatment groups (palbociclib plus letrozole minus placebo-letrozole), where positive values indicate improvement from baseline and negative values indicate deterioration from baseline.

Table 10: Patient-reported pain outcomes in the PALOMA-1 trial (for combined Cohorts) as measured by the Modified Brief Pain Inventory- Short Form (Pain Severity and Pain Interference Scales).[6]

Mean Change (SE) from Baseline in mBPI-sf	Palbociclib + Letrozole	Letrozole alone
n	76	74
Pain Severity Scale	0.4 (0.29)	0.2 (0.32)
Pain at its worst in the last 24 hours	0.6 (0.42)	0.1 (0.42)
Pain at its least in the last 24 hours	0.4 (0.27)	0.4 (0.27)
Pain on the average	0.2 (0.33)	0.2 (0.34)
Pain right now	0.3 (0.35)	0.1 (0.36)
Mean Difference (95% CI) *p-value	0.2 (-0.7-1.0) p=0.69	
n	76	74
Pain Interference Scale	0.8 (0.34)	0.4 (0.30)
General activity	1.1 (0.40)	0.2 (0.31)
Mood	0.8 (0.50)	0.2 (0.36)
Walking ability	0.8 (0.46)	0.1 (0.35)
Normal work	0.7 (0.48)	0.3 (0.39)
Relations	0.8 (0.32)	0.8 (0.32)
Sleep	0.6 (0.43)	0.3 (0.35)
Enjoyment of life	0.8 (0.46)	0.6 (0.41)
Mean Difference (95% CI) *p-value	0.4 (-0.5-1.3) p=0.33	
Abbreviations: CI - confidence interval; mBPI-sf- modified Brief Pain Inventory-Short Form; number; SE - standard error.		
Notes: *p-values are based on a 2-sample t-test.		

Harms Outcomes

Adverse Events

Considering both PALOMA trials, palbociclib-letrozole combined treatment was associated with a greater frequency of both all grade and grade 3-4 AEs compared to letrozole, with grade 3-4 neutropenia being the most frequently reported AE (range, 54%-66%, versus 4%-13% with letrozole). Infections, leucopenia and fatigue were also more common with combined treatment. In both trials, compared to letrozole alone, treatment interruptions, dose/cycle delays and permanent treatment discontinuation were also more prevalent in patients receiving palbociclib-letrozole.

PALOMA-2[1,2]

Adverse event data by preferred terms are summarized in Tables 11 and 12, and include all-causality treatment emergent AEs, treatment-related treatment emergent AEs (TRAE), as well as AEs associated with dose reductions and permanent discontinuation of treatment.

All-Causality Treatment Emergent Adverse Events

All-causality AEs (Table 11) of any grade were reported in 99% and 96% of patients in the palbociclib-letrozole and placebo-letrozole treatment groups, respectively. The majority of these were grade 3-4 in the palbociclib-letrozole group (76%), and grade 1-2 (69%) in the placebo-letrozole group. The AEs that occurred most frequently (>20% of patients)

with palbociclib-combined treatment, versus control therapy, included the following: neutropenia (grade 3-4, 55% versus <1%), infections (grade 1-2, 53% versus 38%), fatigue (grade 1-2, 36% versus 27%), nausea (grade 1-2, 35% versus 24%), alopecia (grade 1-2, 33% versus 16%), diarrhea (grade 1-2, 25% versus 18%), dyspnea (grade 1-2, 14% versus 12%) and cough (grade 1-2, 25% versus 19%). Placebo-letrozole treatment was associated with a higher frequency of hot flush (grade 1-2, 31% versus 21%), headache (grade 1-2, 24% versus 21%), and back pain (grade 1-2, 22% versus 20%). Serious AEs (SAEs), according to investigator assessment, were also higher with palbociclib-letrozole treatment at 20% versus 13% with placebo-letrozole. Most SAEs occurred in <1% of patients with the exception of infections (4.3%) and febrile neutropenia (2%).

AEs lead to dose reductions in 36% and 1.4% of patients in the palbociclib-letrozole and placebo-letrozole treatment groups, respectively. The most common AEs associated with dose reductions with palbociclib treatment included neutropenia (24%), asthenia (1.6%), febrile neutropenia (1.4%), and fatigue (1.1%). No single AE was associated with dose reductions in the placebo-letrozole treatment group.

AEs leading to permanent treatment discontinuation (of either palbociclib and letrozole or both) occurred in 9.7% of patients treated with palbociclib-letrozole compared to 5.9% of patients treated with placebo-letrozole. The specific AEs that lead to permanent discontinuation were mostly single-events in both treatment groups and included neutropenia (1.1%) and alanine aminotransferase increased (0.7%) in the palbociclib-letrozole group and fatigue (0.9%) in the placebo-letrozole arm group.

Treatment-related Treatment Emergent Adverse Events

Adverse events attributed to treatment (TRAE) are summarized in Table 12. Considering all grades, a large majority of patients in both treatment groups experienced a TRAE. The majority of these were grade 3-4 in patients treated with palbociclib-combined treatment and grade 1-2 in patients receiving placebo-letrozole. The most common TRAE (>20% of patients) observed in the palbociclib-letrozole group included neutropenia (grade 3-4), alopecia (grade 1-2), fatigue (grade 1-2), leucopenia (grade 3-4) and nausea (grade 1-2). In the placebo-letrozole group, hot flush (grade 1-2) and arthralgia (grade 1-2) were the most common TRAE. Serious TRAE were also higher in the palbociclib-letrozole treatment group (5%) compared to placebo-letrozole (1%) but occurred with much lower frequency.

Deaths

During the treatment phase of the trial, which includes day 1 of treatment through to 28 days after the last dose of study drug, there were 10 (2.3%) deaths and 4 (1.8%) deaths reported in the palbociclib-letrozole and placebo-letrozole treatment groups, respectively. At the data cut-off date (February 26, 2016), an additional 85 (19.1%) and 34 (15.3%) deaths, respectively, had occurred and the majority were deemed related to ABC. It was reported that one study death (pulmonary embolism/respiratory failure) in the placebo arm was considered attributable to study treatment.

PALOMA-1[3]

Adverse events data, which were reported for all patients receiving at least one dose of study medication (n=160), are summarized in Table 11. Adverse events of any grade occurred in 99% of patients treated with palbociclib-letrozole and 84% of patients treated with letrozole alone. The AEs occurring more frequently with combined treatment included neutropenia (all grade, 75% versus 5%), leucopenia (all grade, 43% versus 3%) and fatigue (all grade, 41% versus 23%). No cases of neutropenic fever were reported with combined treatment despite the elevated cytopenias observed in this group. Anemia (all grade, 35% versus 6%), nausea (all grade, 25% versus 13%) and alopecia (all grade, 22% versus 3%) also occurred more frequently with palbociclib-letrozole. The majority of these events were low-grade with the exception of neutropenia (grade 3-4, 54% versus 1%). The incidence of all grade 3-4 events was 76% in the palbociclib-letrozole group and 21% in the letrozole alone group.

Serious adverse events were reported at 8% in the palbociclib-letrozole group and these included pulmonary embolism, back pain and diarrhea. The number of SAEs occurring in the letrozole group was unclear from the trial publication; however, the trial record indicates the incidence of SAEs in the letrozole arm was 6%.[6] It is unclear which specific events contributed to this rate owing to the definition used.

Adverse events lead to treatment interruption in 13% and 3% of patients treated with palbociclib-letrozole and letrozole alone, respectively. In the palbociclib group, AEs lead to a delay in the start of treatment in 45% of patients, dose reductions in 40%, and treatment discontinuation in 13%. Treatment discontinuation was 3% in the letrozole alone group.

Deaths

One death occurred during the trial in the palbociclib-letrozole group, which was attributed to disease progression. No treatment-related deaths were reported.

Table 11: All-causality treatment emergent adverse events[A] in the PALOMA trials.

AE, n (%)	PALOMA-2[1,2]				PALOMA-1[3]			
	Palbociclib + Letrozole n=444		Placebo + Letrozole n=222		Palbociclib + Letrozole n=83		Letrozole alone n=77	
Any grade AE	439 (99)		212 (96)		82 (99)		65 (84)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Any AE	93 (21)	336 (76)	154 (69)	54 (24)	19 (23)	63 (76)	49 (64)	16 (21)
Neutropenia	49 (11)	245 (55)	5 (2)	2 (<1)	17 (20)	45 (54)	3 (4)	1 (1)
Infections	235 (53)	29 (7)	84 (38)	7 (3)	NR	NR	NR	NR
Leucopenia	40 (9)	66 (15)	1 (<1)	0	20 (24)	16 (19)	2 (3)	0
WBC count decreased	26 (12)	46 (10)	4 (2)	0	NR	NR	NR	MR
Neutrophil count decreased	20 (5)	67 (15)	6 (3)	1 (<1)	NR	NR	NR	NR
Fatigue	158 (36)	8 (2)	60 (27)	1 (<1)	30 (36)	4 (5)	17 (22)	1 (1)
Anemia	79 (18)	24 (5)	16 (7)	4 (2)	24 (29)*	5 (6)*	4 (5)*	1 (1)*
Nausea	155 (35)	1 (<1)	54 (24)	4 (2)	19 (23)	2 (2)	9 (12)	1 (1)
Arthalgia	145 (33)	3 (<1)	74 (33)	1 (<1)	18 (22)	1 (1)	10 (13)	2 (3)
Alopecia	146 (33)	0	35 (16)	0	18 (22)**	NA	2 (3)**	NA
Diarrhea	110 (25)	6 (1)	40 (18)	3 (1.4)	14 (17)	3 (4)	8 (10)	0
Hot flush	93 (21)	0	68 (31)	0	17 (21)	0[B]	9 (12)	NA[B]
Thrombocytopenia	62 (14)	7 (2)	3 (1)	0	12 (14)	2 (2)	1 (1)	0
Decreased appetite	63 (14)	3 (<1)	20 (9)	0	12 (14)	1 (1)	5 (6)	0
Dyspnea	61 (14)	5 (1)	27 (12)	3 (1)	11 (13)	2 (2)	5 (6)	1 (1)
Insomnia	66 (15)	0	26 (12)	0	NR	NR	NR	
Nasopharyngitis	62 (14)	0	22 (10)	0	13 (16)	0	8 (10)	0
Rash	59 (13)	2 (<1)	22 (10)	0	NR	NR	NR	
Back pain	90 (20)	6 (1)	48 (22)	0	11 (13)	1 (1)	11 (14)	1 (1)
Headache	94 (21)	1 (<1)	54 (24)	4 (2)	12 (14)	0	8 (10)	0
Vomiting	67 (15)	2 (<1)	34 (15)	3 (1)	12 (14)	0	2 (3)	1 (1)
Asthenia	65 (15)	10 (2)	26 (12)	0	9 (11)	2 (2)	3 (4)	0
Bone pain	NR	NR	NR	NR	8 (10)	2 (2)	3 (4)	0
Constipation	84 (19)	2 (<1)	33 (15)	1 (<1)	10 (12)	0	7 (9)	0
Cough	111 (25)	0	42 (19)	0	10 (12)	0	8 (10)	0
Stomatitis	67 (15)	1 (<1)	13 (6)	0	10 (12)	0	2 (3)	0
Epistaxis	NR	NR	NR	NR	9 (11)	0	1 (1)	0
Influenza	NR	NR	NR	NR	8 (10)	1 (1)	1 (1)	0
Muscoloskeletal pain (myalgia)	53 (12)	0	20 (9)	0	8 (10)	1 (1)	5 (6)	0
Abdominal pain	46 (10)	4 (9)	12 (5)	0	NR	NR	NR	NR
Oedema peripheral	50 (11)	0	14 (6)	0	NR	NR	NR	NR
Dysgeusia	45 (10)	0	11 (5)	0	NR	NR	NR	NR
Dyspepsia	41 (9)	0	26 (12)	1 (<1)	NR	NR	NR	NR
Upper respiratory tract infection	59 (13)	0	25 (11)	0	8 (10)	1 (1)	2 (3)	0
Dry skin	55 (12)	2 (<1)	13 (6)	0	NR	NR	NR	NR
Pyrexia	55 (12)	0	19 (9)	0	NR	NR	NR	NR
Dizziness	60 (14)	2 (<1)	33 (15)	0	8 (10)	0	3 (4)	0
Peripheral neuropothy	NR	NR	NR	NR	8 (10)	0	4 (5)	0
Oropharyngeal pain	NR	NR	NR	NR	8 (10)	0	1 (1)	0
Pain in extremity	67 (15)	1 (<1)	36 (16)	3 (1)	8 (10)	0	6 (8)	0
Anxiety	36 (8)	0	25 (11)	0	NR	NR	NR	NR
Any SAE	87 (20)		28 (13)		7 (8)[C]		5 (6)[D]	
AEs leading to treatment discontinuation	43 (10)		13 (6)		11 (13)[E]		2 (3)[F]	

Abbreviations: AE - adverse events; **n**= number; SAE - serious adverse event; WBC - white blood cell.

Notes:

[A] Most common all-cause adverse events that occurred in at least 10% of patients in the safety population by preferred term and maximum CTCAE grade.

[B] No grade 3 hot flashes; grade 4 data not available.

[C] Serious adverse events were pulmonary embolism (3 patients), back pain (two patients), and diarrhea (two patients). Of note, two other sources [5,6] report the rate of any serious events to be higher at 21.7% (18/83). One patient had a serious adverse event that was deemed treatment-related (colitis ischemic).[5]
[D] Source: ClinicalTrials.gov trial record.[6]
[E] Of these patients, six (7%) discontinued due to a treatment-related adverse event.
[F] Of these patients, two (2%) discontinued due to a treatment-related adverse event.
* Difference in frequency between trial arms was reported as statistically significant (two-sided p<0.0001).
** Difference in frequency between trial arms was reported as statistically significant (two-sided p=0.0002).

Table 12: Treatment-related, treatment emergent adverse events[A] in the PALOMA-2 trial.

TRAE, n (%)	PALOMA-2[2]			
	Palbociclib + Letrozole n=444		Placebo + Letrozole n=222	
Any grade TRAE	428 (96)		179 (81)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Any TRAE	109 (25)	319 (72)	165 (74)	13 (6)
Neutropenia	46 (10)	245 (55)	4 (2)	2 (<1)
Leucopenia	62 (14)	109 (25)	3 (1)	0
Fatigue	128 (29)	6 (1)	44 (20)	0
Alopecia	140 (32)	0	34 (15)	0
Stomatitis	58 (13)	1 (<1)	10 (5)	0
Nausea	95 (21)	1 (<1)	36 (16)	1 (<1)
Arthralgia	86 (19)	1 (<1)	48 (22)	0
Anemia	66(15)	15 (3)	13 (6)	1 (<1)
Infections	77 (17)	8 (2)	16 (7)	1 (<1)
Neutrophil count decreased	16 (4)	67 (15)	5 (2)	1 (<1)
Hot flush	79 (18)	0	62 (38)	0
WBC decreased	25 (6)	46 (10.4)	3 (1)	0
Diarrhea	65 (15)	1 (<1)	24 (11)	2 (<1)
Thrombocytopenia	34 (8)	6 (1)	2 (<1)	0
Asthenia	46 (10)	9 (2)	19 (9)	0
Rash	35 (8)	2 (<1)	9 (4)	0
Decreased appetite	43 (10	1 (<1)	10 (5)	0
Dry skin	41 (9)	0	11 (5)	0
Mucosal inflammation	35 (8)	3 (<1)	7 (3)	
Dysgeusia	37 (8)	0	9 (4)	0
Headache	37 (8)	0	23 (10)	0
Constipation	34 (8)	1 (<1)	14 (6)	0
Myalgia	35 (8)	0	12 (5)	0
Vomiting	32 (7)	0	11 (5)	0
Alanine aminotransferase increased	22 (5)	7 (2)	6 (3)	0
Aspartate aminotransferase increased	23 (5)	7 (2)	6 (3)	0
Epistaxis	28 (6)	0	6 (3)	0
Dizziness	27 (6)	0	15 (7)	0
Platelet count decreased	25 (6)	1 (<1)	1 (<1)	0
Pruritus	25 (6)	1 (<1)	5 (2)	0
Pain in extremity	25 (6)	0	9 (4)	0
Insomnia	24 (5)	0	7 (3)	0
Back pain	17 (4)	0	13 (6)	0
Any SAE	24 (5)		2 (1)	

Abbreviations: TRAE - treatment-related adverse events; n= number; SAE - serious adverse event

Notes:
[A] **Most common treatment-related adverse events reported by ≥5% of patients in the safety population; includes data up to 28 days after last dose of study drug.**

6.4 Ongoing Trials

One ongoing RCT was identified that met the eligibility criteria of this review. PALOMA-4 is similar in design to the PALOMA-2 trial, but will assess palbociclib-letrozole compared to placebo-letrozole in an age restricted (18 to 70 years) Asian patient population.[25]

Table 13: Ongoing trials of palbociclib in combination with endocrine therapy versus endocrine therapy alone in post-menopausal women with ER+/HER2- ABC.

Trial Design	Key Inclusion Criteria	Interventions and Comparators	Outcomes
Trial NCT02297438 (PALOMA-4) Multicentre (49 sites), double-blind randomized phase 3 trial Start date: March 2015 Expected primary completion date: October 2017 Expected completion date: October 2017 Status: Ongoing (recruiting patients) Estimated enrolment: 330 Sponsor: Pfizer	• 18 to 70 years • Asian post-menopausal women with locoregionally recurrent or metastatic disease not amenable to curative therapy. • Confirmed ER+, HER2- • No prior systemic anti-cancer therapy for advanced ER+ disease. • Measurable disease per RECIST or bone-only disease • ECOG 0-1 • Adequate organ function • No prior neoadjuvant or adjuvant treatment with letrozole or anastrozole with disease recurrence while on or within 12 months of completing treatment. • No prior treatment with any CDK 4/6 inhibitor • No uncontrolled or symptomatic CNS metastases • No symptomatic visceral spread at risk of complication in the short-term.	Palbociclib + Letrozole Palbociclib 125 mg, orally once daily on days 1-21 of every 28 day cycle followed by 7 days off treatment; and letrozole 2.5 mg, orally once daily continuously vs. Placebo + Letrozole: Placebo 125 mg, orally once daily on days 1-21 of every 28 day cycle followed by 7 days off treatment; and letrozole 2.5 mg, orally once daily continuously	*Primary:* • PFS *Secondary:* • Overall survival • Objective response • Duration of response • QOL (EQ-5D, FACT-B)

Abbreviations: ABC - advanced/metastatic breast cancer; **CDK** - cyclin dependent kinase; **CNS** - central nervous system; **CR** - complete response; **ECOG** - Easter Cooperative Oncology Group; **ER** - estrogen receptor; **EQ-5D** - Euro Quality of Life-5D; **FACT-B** - Functional Assessment of Cancer Therapy - Breast; **HER2** - human epidermal growth factor receptor 2; **PFS** - progression-free survival; **PR** - partial response; **RECIST** - Response Evaluation Criteria in Solid Tumors; **SD** - stable disease; **QOL** - quality of life.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of palbociclib in combination with standard endocrine therapy as first-line treatment in post-menopausal women with estrogen-receptor (ER+) and human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer (ABC):

- Critical appraisal of a network meta-analysis (NMA) comparing palbociclib with other therapies as first-line treatment in post-menopausal women with ER+ and HER2- ABC.

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

7.1 Critical Appraisal of Network Meta-analysis

7.1.1 Objective

To summarize and critically appraise the methods and results of the manufacturer-submitted NMA[26] comparing palbociclib with other therapies as first-line treatment in post-menopausal women with ER+ and HER2- ABC.

7.1.2 Findings

Rationale
Since multiple endocrine therapies are available for first-line treatment of ER+/HER2- ABC, the objective of the NMA was to compare palbociclib-letrozole with other available treatment options that have not been directly compared in randomized trials. An NMA was conducted in order to derive estimates of treatment effect among the treatments that have not been directly compared.

Methods
The authors cited using the methods of CADTH for conducting the NMA. A proposal was developed in advance, which pre-specified the PICOS elements (i.e., population, interventions, comparators, outcomes and study designs) of interest. Eligible treatment comparators included anastrozole (1mg daily), letrozole (2.5mg daily), tamoxifen (20mg daily) and exemestane (25mg daily). These regimens were chosen because they are currently publically funded as first-line treatments in Canada. At the suggestion of pCODR, other comparators, specifically other combination therapies, were considered in a sensitivity analysis and included treatments either approved for use in Canada but not publically funded (i.e., fulvestrant 250mg or 500mg intramuscular injection (IM) monthly, anastrozole 1mg daily + fulvestrant 250mg IM monthly with loading dose), approved but not commonly used (tamoxifen 40mg daily), or used in later lines of treatment and lacking proper evaluation in RCTs (available data are from a retrospective subgroup analysis) in the first-line setting (i.e., everolimus 10mg daily + exemestane 25mg daily). The results of the sensitivity analysis are included as an expanded NMA. The outcomes of interest were progression-free survival or time-to-progression (PFS/TTP) and overall survival (OS). Other important outcomes of interest, including health-related quality of life (QOL) and safety, were not considered in the review (as outlined in the PICOs framework criteria).

The evidence informing the NMA was identified through a systematic review of all randomized trials, however, the full systematic review in its entirety was not provided to pCODR. Details were provided on the eligibility criteria used, the specific literature search strategies performed, and the methods used for trial selection and data extraction. Included trials were assessed for quality (risk of bias) using the quality checklist of NICE. It is unclear, however, how the results of the quality assessment were actually used in the NMA. Visual diagrams of the evidence networks for each outcome were provided. The results of individual trials were provided and presented as hazard ratios and 95% confidence intervals.

The NMA used Bayesian methods to estimate relative measures of treatment effect. For each pairwise comparison (direct and indirect), hazard ratios (HR) and 95% credible intervals (CrI) were used to measure the association between treatments for efficacy. Other effect measures, although not the focus of this report, were reported and included the following:

- Mean rank with 95% credible intervals (where values close to 1 indicate better treatment)
- Probability best, second best, etc.
- SUCRA (surface under the cumulative ranking curve) which is an estimate of ranking and uncertainty (expressed as a percentage, shows the relative probability of an intervention being among the best options)

The analysis was planned using both random and fixed effects models; however, the authors noted, appropriately, that the presence of a network largely comprised of single-study connections between interventions limits the ability to reliably estimate between study variance. As a result, the authors focused on the fixed effects results but reported findings from both analyses. Consistency between direct and indirect evidence was also assessed and these investigations showed no inconsistency for either outcome of interest. Possible sources of heterogeneity were considered in advance of performing analyses and investigated using statistical (e.g., sensitivity analyses) and non-statistical (e.g. graphical and tabular summaries) approaches with the results of these inquiries also reported. Possible sources of heterogeneity included the following:

- Percentage of patients with prior endocrine therapy or chemotherapy for ABC
- Percentage of patients hormone-receptor positive (HR+)
- Variation in defining PFS-TTP endpoints, as well as variation in observed median PFS/TTP and OS in a given intervention group when multiple studies were present
- Inclusion of crossover studies
- Blinding
- Inclusion of older age patients
- Inclusion of PALOMA-1 trial (using HRs obtained by investigator assessment versus blinded independent central review)

Results

The literature search identified a total of 3649 records that were screened for eligibility. The screening process narrowed the results down to 331 RCTs requiring full-text review. Of these, 8 trials met the eligibility criteria of the NMA,[e] however

[e]pCODR suggested the Submitter consider inclusion of PALOMA-2 into the NMA; however, contrary, to what is indicated in the updated NMA report (section 3.1 study selection), pCODR did not request that the data for PALOMA-2 replace the PALOMA-1 data in the primary NMA analysis. Both trials met the inclusion criteria of the review and should have been included in the primary NMA. In light of the

one trial did not report outcome data, which left seven trials (consisting of 3360 patients) for inclusion into the primary NMA of each outcome. A brief summary of the characteristics of these trials was provided in the NMA, and has been reproduced in Table 14. The results of the individual trials are summarized in Table 15. The expanded NMA (i.e., sensitivity analysis) included an additional six trials; the characteristics and results of these trials have also been summarized in Tables 14 and 15, respectively.

Primary Evidence Network Meta-Analysis
For PFS/TTP, the primary evidence NMA was comprised of five direct comparisons, with single trials informing three of these comparisons, giving 10 pairwise comparisons in total. Figure 1 depicts the primary evidence network for PFS/TTP. For OS, the evidence network was also comprised of five direct comparisons, with single trials informing three of these comparisons, and a total of 10 pairwise comparisons .The evidence network for OS is shown in Figure 2.

The primary evidence NMA found a statistically significant difference in PFS/TTP in favour of palbociclib-letrozole relative to letrozole, anastrozole, exemestane, and tamoxifen (Table 16). All sensitivity analyses performed indicated the PFS results were robust to differences in the patient or study characteristics assessed. Although a trend towards the palbociclib-letrozole group was observed, no statistically significant differences in OS were detected between palbociclib-letrozole relative to letrozole, anastrozole, exemestane or tamoxifen.

Expanded Evidence Network Meta-Analysis Sensitivity Analysis
For PFS/TTP, the expanded evidence NMA was comprised of nine direct comparisons, with single trials informing six of these comparisons, giving a total of 36 pairwise comparisons (Figure 3). For OS, the expanded network included 10 direct comparisons, with single trials informing seven of these comparisons, and providing a total of 45 pairwise comparisons (Figure 4).

The results from the expanded NMA showed palbociclib-letrozole was associated with superior PFS/TTP compared to all comparator regimens examined with the exception of combined therapy with everolimus-exemestane (HR=1.24, 95% CrI, 0.71-2.16) and high-dose fulvestrant (HR=0.74, 95% CrI, 0.47-1.18) where no difference between regimens was observed. No differences in OS were detected between palbociclib-letrozole versus the other regimens examined.

methodological issues associated with the PALOMA-1 trial it would be appropriate to use the results of the blinded independent central review analysis for this trial in the primary NMA analysis (opposed to the investigator assessment analysis). The updated NMA includes the PALOMA-1 trial data in sensitivity analyses for the primary endpoint of PFS and the main analysis for OS, since PALOMA-2 OS data are presently immature.

Table 14: Summary of individual trials included in the manufacturer submitted network met-analysis for the primary and expanded network analyses.

Trial Publication	n	Blinding	Patient Population*				Prior adjuvant endocrine therapy	Prior metastatic therapy %		Intervention and Comparator
			Line of Treatment	ER/PgR+	Metastases	Median age in years		Endocrine	Chemotherapy	
Primary Evidence Network										
Bonneterre 2000	668	DB	1st	45%	34% visceral 31% bone 15% bone only	67	8%	0%	0%	Anastrozole vs. tamoxifen
Finn 2016 (PALOMA-2)	666	DB	1st	100%	49% visceral NR bone NR bone only	62	43%	0%	0%	Palbociclib-letrozole vs. placebo-letrozole
Finn 2015 (PALOMA-1)[A]	165	OL	1st	100%	48% visceral 18% bone 18% bone only	64	33%	0%	0%	Palbociclib-letrozole vs. letrozole
Iwata 2013	292	DB	1st	74%	50% visceral 27% bone 27% bone only	64	NR	0%	4%	Exemestane vs. anastrozole
Llombart-Cussac 2012	103	OL	1st/2nd	100%	52% visceral NR bone NR bone only	72	50%	0%	9.7%	Exemestane vs. anastrozole
Mouridsen 2001	907	DB	1st/2nd	100%	44% visceral 30% bone 16% bone only	65	18%	0%	0%	Letrozole vs. tamoxifen
Nabholtz 2000	353	DB	1st	89%	48% visceral 60% bone 25% bone only	68	12%	0%	4.3%	Anastrozole vs. tamoxifen
Paridaens 2008	371	OL	1st/2nd	93%	47% visceral 35% bone 12% bone only	63	21%	0%	4.3%	Exemestane vs. tamoxifen
Expanded Evidence Network (Sensitivity Analysis)										
Beck 2014[B]	NR	DB	1st	100%	45% visceral 69% bone 25% bone only	61	100%	0%	0%	Everolimus-exemestane vs. exemastane

Trial Publication	n	Blinding	Patient Population*				Prior adjuvant endocrine therapy	Prior metastatic therapy %		Intervention and Comparator
			Line of Treatment	ER/PgR+	Metastases	Median age in years		Endocrine	Chemotherapy	
Yardley 2013[B]	NR	DB	1st/2nd	100%	59% visceral 77% bone 21% bone only	62	NR	NR	0%	Everolimus-exemestane vs. exemestane
Bergh 2012	NR	OL	1st	100%	50% visceral NR bone 26% bone only	64	68%	0%	0%	Anastrozole-fulvestrant vs. anastrozole
Mehta 2012	NR	NR	1st	100%	50% visceral NR bone 22% bone only	65	40%	0%	0%	Anastrozole-fulvestrant vs. anastrozole
Robertson 2012 / Ellis 2015	NR	OL	1st	100%	52% visceral NR bone 9% bone only	67	25%	0%	0%	Fulvestrant HD vs. anastrozole
Howell 2004	NR	DB	1st	78%	52% visceral NR bone 9% bone only	67	23%	0%	0%	Tamoxifen vs. fulvestrant
Milla-Santos 2003	NR	NR	1st	100%	NR visceral 40% bone NR bone only	60	0%	0%	0%	Tamoxifen HD vs. anastrozole

Abbreviations: DB - double blind; ER - estrogen receptor; OL - open-label; NR - not reported; PgR - progesterone receptor; vs. versus.

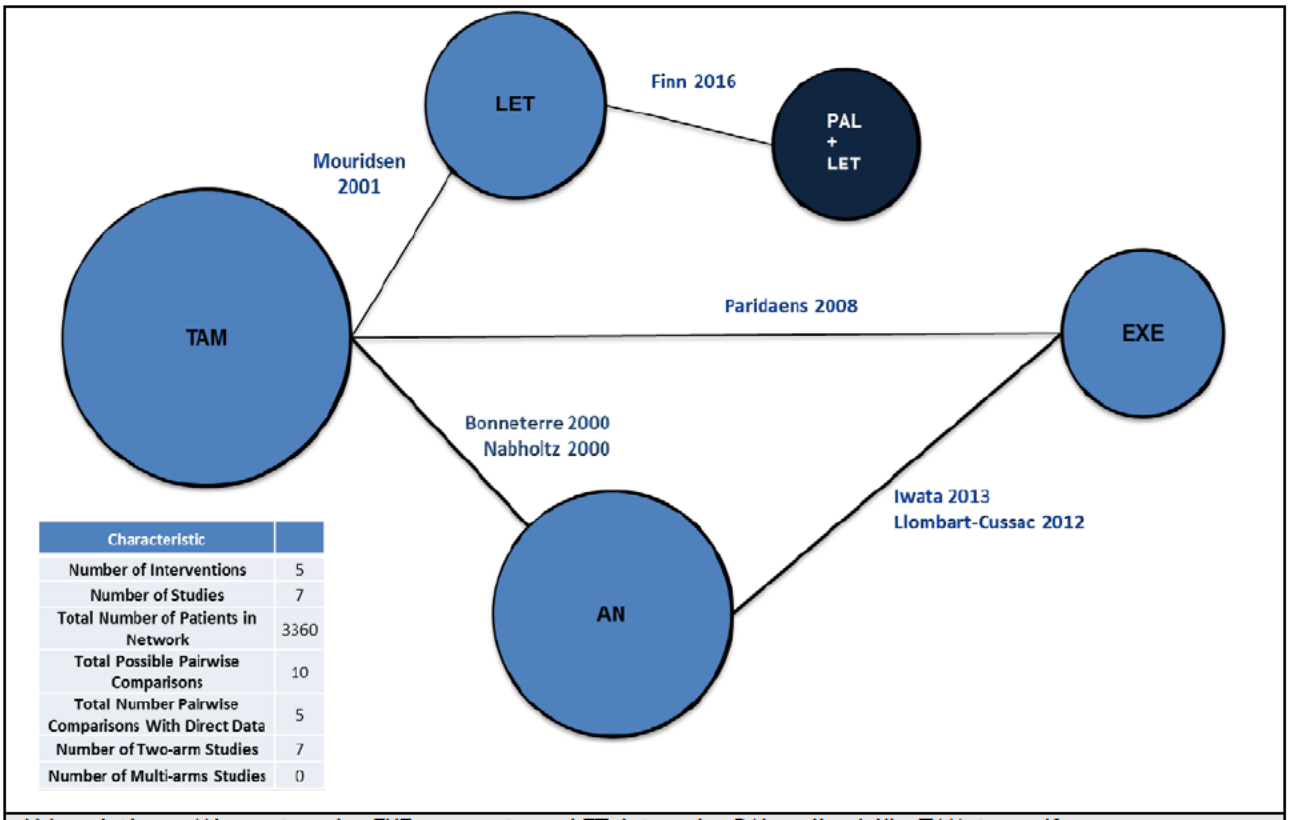
Notes:
[A] The PALOMA-1 trial was included in sensitivity analyses for PFS/TTP and the main analysis of OS.
[B] Beck 2014 and Yardley 2013 are the same trial; Beck 2014 is a subgroup analysis of the first-line patients included in the trial.

Table 15: Summary of progression-free survival (or time-to-progression) and overall survival data from individual trials included in the manufacturer-submitted network meta-analysis.

Trial Publication	Treatment Comparison	N	Duration of Follow-up in months		PFS/TTP		OS	
			PFS/TTP	OS	HR	95% CI*	HR	95% CI*
Primary Evidence Network								
Finn 2016 (PALOMA-2)	Palbociclib-letrozole vs. placebo-letrozole	666	23	NA	0.58	0.46-0.72	NA	
Finn 2015 (PALOMA-1)[A]	Palbociclib-letrozole vs. letrozole	165	NA	28.7	0.49	0.32-0.75	0.81	0.49-1.35
Iwata 2013	Exemestane vs. anastrozole	292	NR	NR	0.99	0.76-1.3	0.94	0.65-1.36
Llombart-Cussac 2012	Exemestane vs. anastrozole	103	9	NR	1.13	0.75-1.72	1.33	0.78-2.25
Mouridsen 2001	Letrozole vs. tamoxifen	907	18	32	0.7	0.6-0.82	1.01	0.9-1.14****
Bonneterre 2000	Anastrozole vs. tamoxifen	668	19	44	1.01	0.79-1.29**	1.06	0.92-1.27***
Nabholtz 2000	Anastrozole vs. tamoxifen	353	18	44	0.69	0.54-0.9**	0.98	0.81-1.23***
Paridaens 2008	Exemestane vs. tamoxifen	371	29	49	0.84	0.67-1.05	1.13	0.85-1.5
Expanded Evidence Network (Sensitivity Analysis)								
Beck 2014[B]	Everolimus-exemestane vs. exemastane	NR	18[C]		0.39	0.25-0.62	NR	
Yardley 2013[B]	Everolimus-exemestane vs. exemastane	NR	18[C]		0.45	0.38-0.54	0.89	0.73-1.1
Bergh 2012	Anastrozole-fulvestrant vs. anastrozole	NR	9[C]		0.99	0.81-1.20	1.0	0.76-1.32
Mehta 2012	Anastrozole-fulvestrant vs. anastrozole	NR	35[C]		0.80	0.68-0.94	0.81	0.65-1.00
Robertson 2012/Ellis 2015	Fulvestrant HD vs. anastrozole	NR	NR		0.63	0.39-1.00	0.70	0.50-0.98
Howell 2004	Tamoxifen vs. fulvestrant	NR	15[C]		0.85	0.69-1.02	0.78	0.61-0.99
Milla-Santos 2003	Tamoxifen HD vs. anastrozole	NR	13[C]		NR[D]		1.56	1.16-2.13

Abbreviations: CI - confidence interval; HD - high-dose; HR = hazard ratio; OS - overall survival; NA - not available; NR - not reported; PFS - progression-free survival; TTP -time-to-progression.

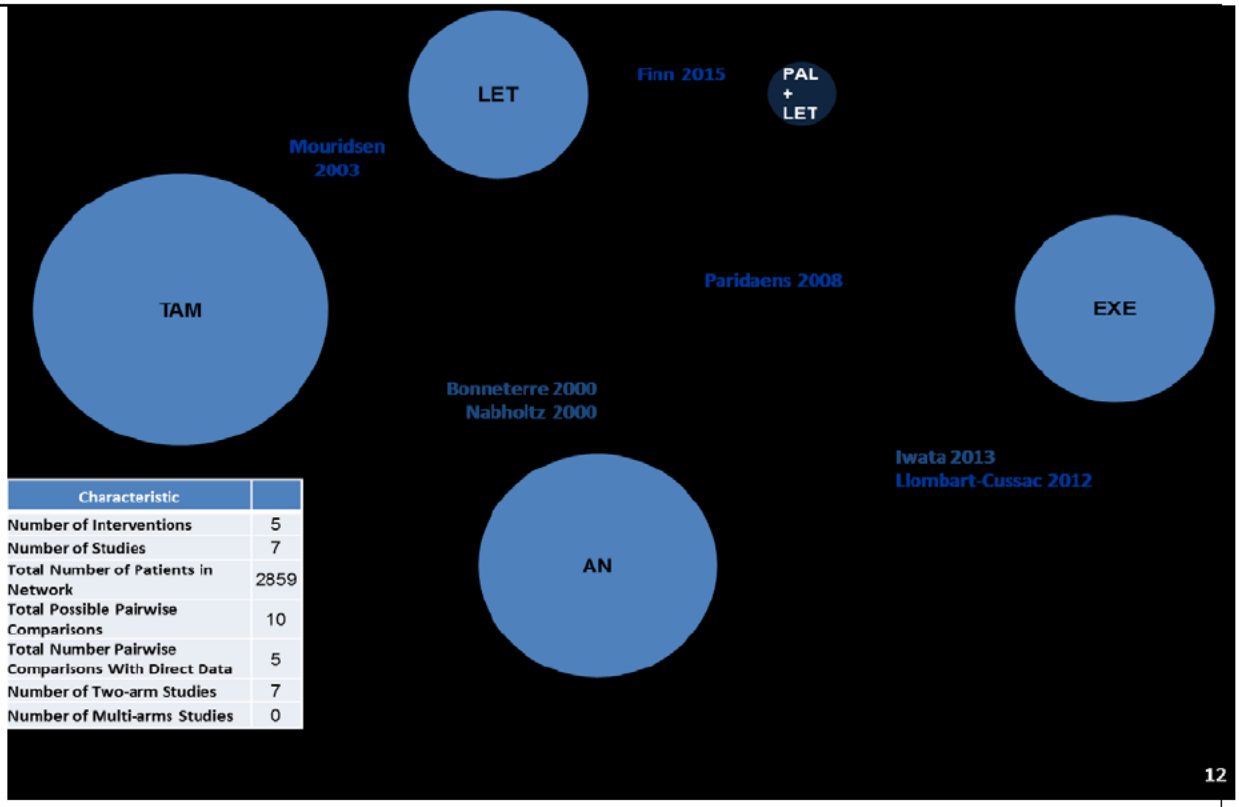
Notes:
* p-values were not reported.
** Confidence intervals were estimated from reported HRs and p-values using methods by Altman (2011).
*** Upper limit of confidence interval was manually calculated using statistical formula.
**** Hazard ratios were calculated using the methods of Tierney (2007).
[A] The PALOMA-1 trial was included in sensitivity analyses of PFS/TTP and the primary analysis of OS.
[B] Beck 2014 and Yardley 2013 are the same trial; Beck 2014 is a subgroup analysis of the first-line patients included in the trial.
[C] The duration of follow-up was not specified for PFS/TTP or OS.
[D] Milla-Santos 2003 only reported PFS in patients who achieved a clinical benefit. This was considered not comparable with the PFS HRs from all other included studies, which reported PFS in all patients who underwent treatment.



Characteristic	
Number of Interventions	5
Number of Studies	7
Total Number of Patients in Network	3360
Total Possible Pairwise Comparisons	10
Total Number Pairwise Comparisons With Direct Data	5
Number of Two-arm Studies	7
Number of Multi-arms Studies	0

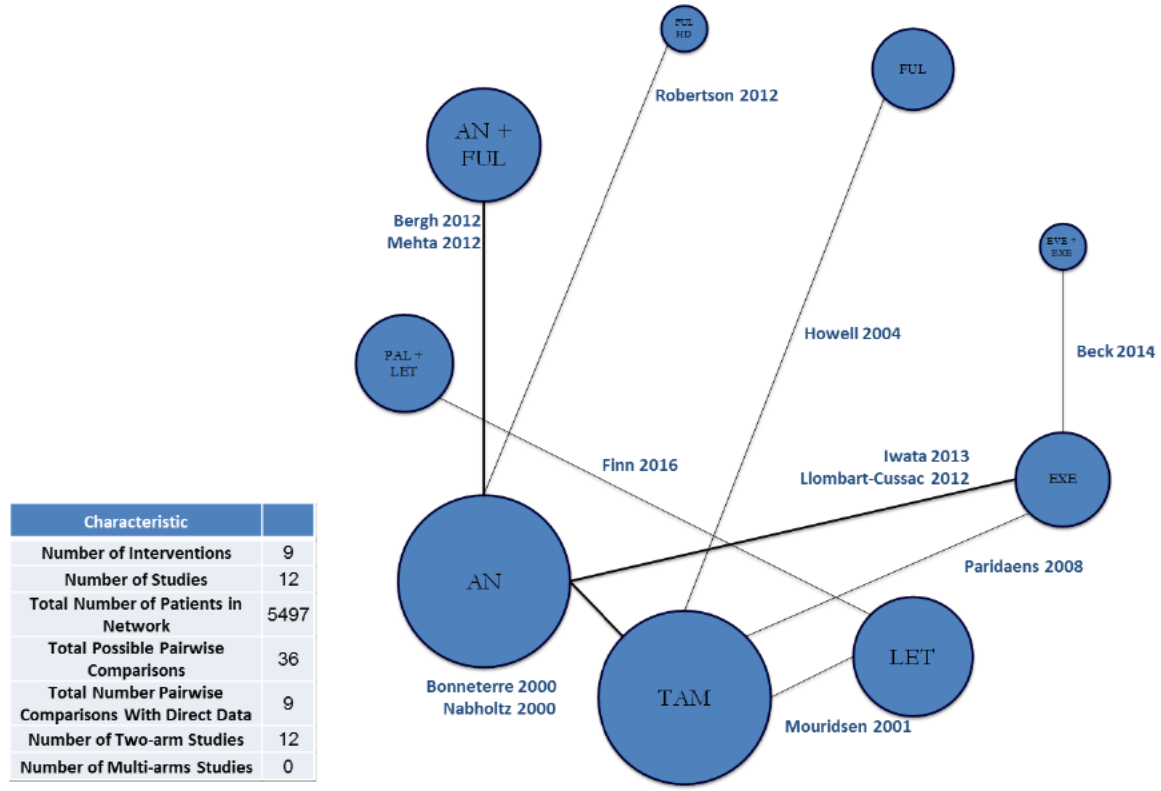
Abbreviations: AN=anastrozole; EXE=exemestane; LET=letrozole; PAL=palbociclib; TAM=tamoxifen

Figure 1:Primary evidence network for progression-free survival/time-to-progression.



Abbreviations: AN=anastrozole; EXE=exemestane; LET=letrozole; PAL=palbociclib; TAM=tamoxifen
* Overall survival (OS) data are immature for the PALOMA-2 trial; OS analyses for this treatment are based on the results from the PALOMA-1 trial.

Figure 2: Primary evidence network for overall survival.

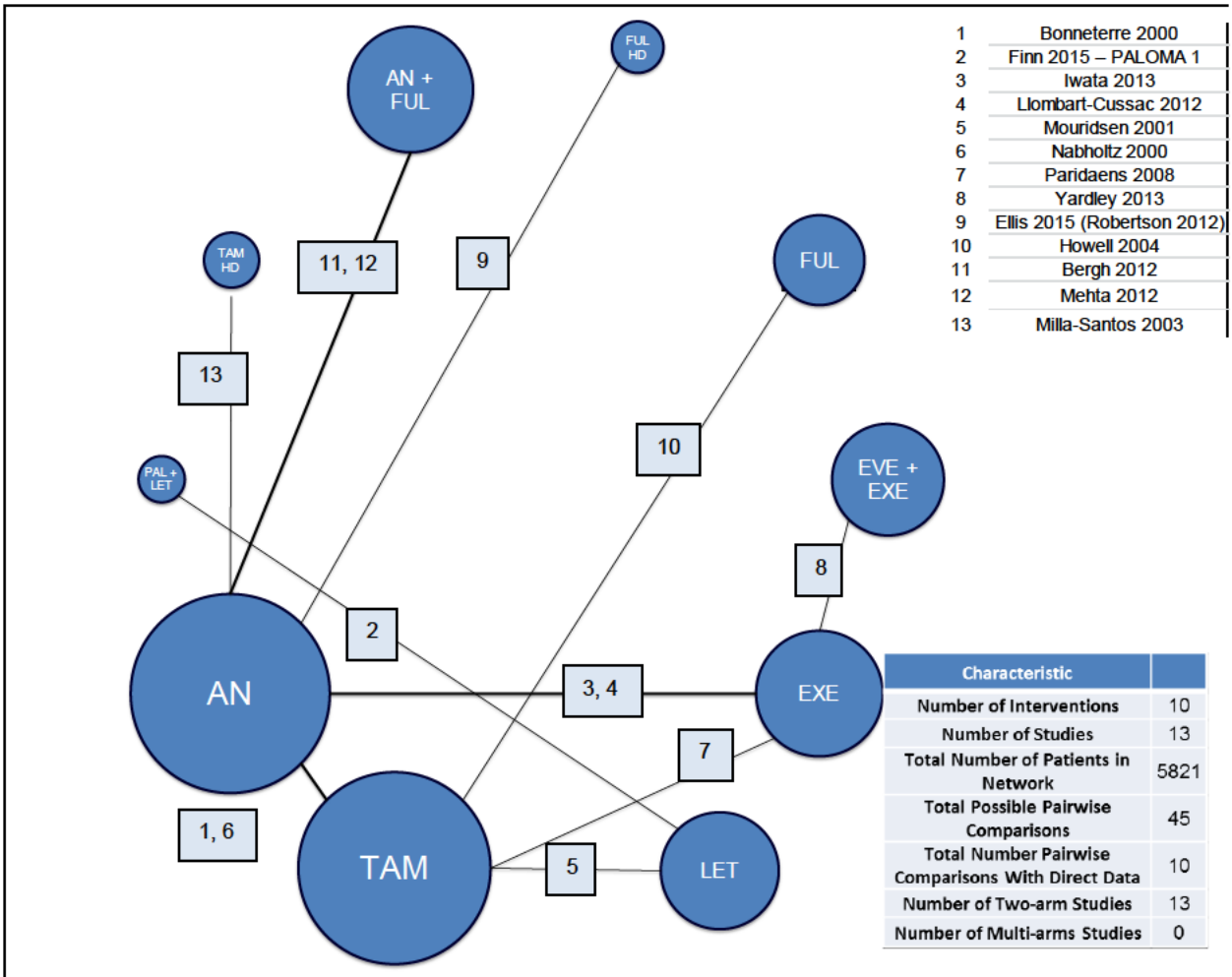


Characteristic	
Number of Interventions	9
Number of Studies	12
Total Number of Patients in Network	5497
Total Possible Pairwise Comparisons	36
Total Number Pairwise Comparisons With Direct Data	9
Number of Two-arm Studies	12
Number of Multi-arms Studies	0

Note: This evidence network includes the addition of the following comparators: everolimus + exemestane (EVE+EXE), fulvestrant (FUL), high dose fulvestrant (FUL HD), and anastrozole + fulvestrant (AN + FUL). Note that FUL and FUL HD are both administered through an intramuscular injection (IM) on days 1, 14, 28 and monthly thereafter with dosages of 250 mg and 500mg, respectively. Also, AN + FUL consists of 1 mg of anastrozole taken daily as well as fulvestrant administered 250 mg IM monthly with a loading dose of 500 mg on day 1, and 250 mg on days 15 and 29.

Abbreviations: PFS=progression-free survival; TTP=time to progression; AN=anastrozole; EXE=exemestane; LET=letrozole; PAL=palbociclib; TAM=tamoxifen; EVE=everolimus; FUL=fulvestrant; HD FUL=high dose fulvestrant.

Figure 3: Expanded evidence network sensitivity analysis for progression-free survival/time-to-progression.



Note: This evidence network includes the addition of the following comparators: everolimus + exemestane (EVE+EXE), fulvestrant (FUL), and high dose fulvestrant (HD FUL). Note that FUL and HD FUL are both administered through an intramuscular injection on days 1, 14, 28 and monthly thereafter with dosages of 250 mg and 500mg, respectively.

Abbreviations: OS=overall survival; AN=anastrozole; EXE=exemestane; LET=letrozole; PAL=palbociclib; TAM=tamoxifen; EVE=everolimus; FUL=fulvestrant; HD FUL=high dose fulvestrant

Figure 4: Expanded evidence network sensitivity analysis for overall survival.

Table 16: Summary of the manufacturer-submitted network meta-analysis results[A] for progression-free survival (or time-to-progression) and overall survival: primary network analysis and expanded network sensitivity analysis.

Treatment Comparison *Palbociclib-letrozole versus:*	PFS/TTP		OS	
	HR*	95% CrI	HR*	95% CrI
Primary Analysis[B]	n=3360		n=2859	
Letrozole	0.59	0.47-0.73	0.82	0.49-1.34
Anastrozole	0.49	0.36-0.67	0.80	0.47-1.35
Tamoxifen	0.41	0.31-0.54	0.82	0.49-1.38
Exemestane	0.48	0.35-0.67	0.74	0.43-1.29
Expanded Network Sensitivity Analysis[C]	n=5497		n=5821	
Everolimus-exemestane	1.24	0.71-2.16	0.84	0.45-1.54
Anastrozole-fulvestrant	0.52	0.38-0.73	0.91	0.51-1.62
Fulvestrant	0.32	0.22-0.46	0.64	0.36-1.15
HD Fulvestrant 500 mg IM	0.74	0.47-1.18	1.15	0.60-2.18
HD Tamoxifen 40mg daily	NA[D]		0.51	0.27-0.96

Abbreviations: ABC - advanced/metastatic breast cancer; **CrI** - credible inverval; **HD** - high-dose; **HR** - hazard ratio; **NA** - not available; **OS** - overall survival; **PFS** - progression-free survival.

Notes:
* HR <1.00 favour palbociclib-letrozole.
[A] Results are based on a fixed-effects analysis.
[B] The primary NMA compared palbociclib-letrozole to therapies (all single-agent) publically reimbursed for first-line treatment of ABC.
[C] The expanded NMA sensitivity analysis compared palbociclib-letrozole to all therapies (single-agent and combination) for which there is RCT-level evidence (includes therapies approved but not publically reimbursed or commonly used in the first-line setting).
[D] The trial by Milla-Santos only reported PFS for patients who achieved a clinical benefit. Therefore HD tamoxifen was not included in the expanded network sensitivity analysis.

Limitations

The quality of the manufacturer-submitted NMA was assessed according to the 2014 ISPOR (International Society of Pharmacoeconomics and Outcomes Research) Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire.[27] The full quality assessment, which can be found in Appendix C, identified a number of limitations associated with the NMA related to relevance and credibility.

Relevance

The relevance of the submitted NMA to the current systematic review is considered insufficient for the following reasons:

- The primary NMA focused on palbociclib-letrozole compared to various single-agent therapies that are approved and publically reimbursed in Canada for first-line therapy, but not to other combination therapy (as currently none are publically reimbursed or commonly used in the first-line setting). It is quite likely, however, that a combination treatment of two effective components (i.e., palbociclib-letrozole) with distinctive pharmacological mechanisms of action is better than monotherapy in terms of efficacy. Randomized data are available on combination treatments (i.e., everolimus-exemestane, anastrozole-fulvestrant) evaluated as first-line treatment in ABC. Therefore, in response to pCODR's critique of the original NMA, the Submitter updated it to include additional

therapies (including other combination therapies) in an expanded NMA sensitivity analysis. This analysis showed PFS/TTP was superior with palbociclib-letrozole compared to anastrozole, tamoxifen 20mg, letrozole, exemestane, fulvestrant 250mg, and anastrozole-fulvestrant, while no difference was observed between palbociclib-letrozole and everolimus-exemestane or high-dose fulvestrant (500mg). While it appears from this post-hoc analysis that PFS benefit is associated with combined therapy consisting of a targeted agent and a hormonal therapy, caution is warranted as the expanded NMA evidence network is limited by single trial connections or small numbers of trials (n≤2), small sample sizes, and the use of data from retrospective subgroup analyses for one of the three trials evaluating combination therapy.

- The submitted NMA did not explore the comparative safety or QOL between palbociclib-letrozole and other therapies, which presumably would be important especially when a combination therapy is compared to a single-agent therapy. The Submitter indicated QOL data were not amenable to NMA because only two trials reported QOL and they used two different assessment instruments. For safety, however, the Submitter suggested pCODR identify relevant adverse events of interest for analysis. As assessment of safety should have been prospectively conducted as part of the systematic review and NMA opposed to a post-hoc synthesis. The original NMA submitted to pCODR did suggest safety analyses were in fact performed separate from efficacy outcomes; however, these safety analyses were not mentioned in the updated version of the NMA.
- It is unclear as to whether the patient populations of included trials in the primary NMA are entirely relevant. The HER2 status of patients was not reported in a majority of trials (five of seven). Further, the percentage of patients with HR status unknown or negative ranged from 7%-55% in four trials; and a proportion of patients (4%-9%), albeit small, were treated in the second-line setting with chemotherapy in four trials. Some of these issues likely stem from the inclusion of older trials into the NMA.

Credibility

The credibility of the NMA results, particularly a statistically significant difference in PFS/TTP between palbociclib-letrozole versus all other single therapies (primary analysis), is considered insufficient for the following reasons:

- There is notable heterogeneity across trials (e.g., proportion of patients HR+, inclusion of 2nd-line patients, blinding, variations in definitions of the PFS/TTP) even though the authors did a range of sensitivity analyses based on trial and patient characteristics. The authors acknowledged the level of heterogeneity present among the trials and the inability to control for all influencing patient and trial factors due to limited available data (or lack thereof) and the structure of the evidence network. Therefore, it is difficult to determine whether the effect estimates obtained were solely due to differences in treatments.
- The full systematic review upon which the NMA was based was not provided to pCODR. This is needed in order to determine whether all relevant trials were identified and appropriately included or excluded from the NMA, and to review the full critical appraisal of individual trials. If included trials are biased then the NMA results may also be biased.

7.1.3 Summary

A manufacturer-submitted NMA, comparing palbociclib-letrozole to other endocrine therapies as first-line treatment in post-menopausal women with ER+ and HER2- ABC, was summarized and critically appraised using the ISPOR Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire. The primary NMA found a statistically significant difference in PFS/TTP in favour of palbociclib-letrozole relative to letrozole, anastrozole, exemestane and tamoxifen. All

sensitivity analyses performed indicated the PFS results were robust to differences in the patient and study characteristics assessed. No differences in OS were demonstrated. An expanded network sensitivity analysis, which was performed post-hoc and included other combination therapies, showed superior PFS/TTP with palbociclib-letrozole compared to anastrozole, tamoxifen, letrozole, exemestane, fulvestrant 250mg, and anastrozole-fulvestrant, while no differences were observed between palbociclib-letrozole and everolimus-exemestane or high-dose fulvestrant (500mg). No differences in OS were observed between any of the regimens examined. The quality assessment judged the overall relevance and credibility of the NMA to be insufficient. The main limitations of the NMA include omission of other combination therapies from the primary NMA (versus only single-agent regimens), failure to include other important outcomes (i.e., adverse events), significant heterogeneity across included trials, and the inability to adjust for the influence of heterogeneity due to constraints in the structure of the evidence networks (e.g., single trial connections or small numbers of trials). The conclusions drawn from the NMA should be interpreted with caution.

8 COMPARISON WITH OTHER LITERATURE

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

9 ABOUT THIS DOCUMENT

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

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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

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

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** October 2015, **Embase** 1974 to 2015 November 19, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches
1	(Palbociclib* or Ibrance* or PD-0332991 or PD-332991 or PD0332991 or PD332991 or "pf 00080665" or pf00080665 or G9ZF61LE7G or 571190-30-2).ti,ot,ab,sh,rn,hw,nm,kf.
2	1 use pmez,cctr
3	*Palbociclib/
4	(Palbociclib* or Ibrance* or PD-0332991 or PD-332991 or PD0332991 or PD332991 or "pf 00080665" or pf00080665 or G9ZF61LE7G or 571190-30-2).ti,ab,kw.
5	or/3-4
6	5 use oemezd
7	2 or 6
8	exp animals/
9	exp animal experimentation/ or exp animal experiment/
10	exp models animal/
11	nonhuman/
12	exp vertebrate/ or exp vertebrates/
13	animal.po.
14	or/8-13
15	exp humans/
16	exp human experimentation/ or exp human experiment/
17	human.po.
18	or/15-17
19	14 not 18

20	7 not 19
21	remove duplicates from 20
22	limit 21 to english language

2. Literature search via PubMed

Search	Add to builder	Query
#3	Add	Search **(#1 AND #2)**
#2	Add	Search **publisher[sb]**
#1	Add	Search **Palbociclib*[tw] OR Ibrance*[tw] OR PD-0332991[tiab] OR PD-332991[tiab] OR PD0332991[tiab] OR PD332991[tiab] OR pf 00080665[tiab] OR pf00080665[tiab] OR G9ZF61LE7G[rn] OR 571190-30-2[rn]**

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 terms: Palbociclib or Ibrance

Select international agencies including:

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

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

Search terms: Palbociclib or Ibrance

Conference abstracts:

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

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

Search terms: Palbociclib or Ibrance / last 5 years

APPENDIX B: DETAILED METHOLODGY OF LITERATURE REVIEW

Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2010, Issue 2) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was palbociclib (Ibrance).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year. The search is considered up to date as of August 29, 2016.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies, clinical trial registries and relevant conference abstracts. Searches of conference abstracts were limited to the last five years. 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 information as required by the pCODR Review Team.

Study Selection

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

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

Quality Assessment

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

Data Analysis

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

Writing of the Review Report

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

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.

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

Appendix C: Appraisal of the manufacturer-submitted network meta-analysis (NMA), comparing palbociclib-letrozole to other therapies,[26] using the ISPOR Questionnaire to assess Relevance and Credibility.[27]

Table 1: Relevance

Item	Description	Strength	Weakness	Can't Answer		
		Yes	No	Not Reported	Insufficient Information	Other Reason
1	Is the population relevant?	Yes	No[A]			
2	Are any critical interventions missing?	No	Yes[B]			
3	Are any relevant outcomes missing?	No	Yes[C]			
4	Is the context (e.g., settings and circumstances) applicable to your population?	Yes	No			

Notes:

[A] The patient populations of the included randomized trials are not entirely relevant:

- The percentage of patients who were hormone-receptor positive was not 100% in all trials (100% in three trials; ranged from 45% to 93% in four trials).
- Three trials included patients treated in the second-line setting; in each of these trials patients received chemotherapy for their advanced/metastatic disease. The manufacturer indicated these patients comprised <10% of patients included in the NMA.
- The HER2 status of included patients was not reported for the majority of trials.
- Some relevancy issues may be a consequence of including older trials into the NMA (three trials were published between 2000 and 2001).

[B] Palbociclib-letrozole was compared to different single-agent therapies and not to other combination therapies in the NMA. Three trials, two comparing anastrozole-fulvestrant to anastrozole alone[28,29] and the other evaluating everolimus-exemestane (retrospective subgroup data from an RCT),[30] were excluded from the primary analysis of both outcomes [progression-free survival/time-to-progression (PFS/TTP) and overall survival (OS)] because the former combination regimen is not reimbursed in Canada and the latter regimen is limited to the results of subgroup analyses, which were ineligible for inclusion into the review. In an update to the original NMA, the Submitter included these trials in sensitivity analyses.

[C] Comparative data on adverse events and/or quality of life were not provided to pCODR although it was indicated that such analyses were performed separately from efficacy outcomes. Inclusion of these outcomes is important when comparing combination therapy to single agents, as increased toxicity is more likely with combination treatment.

Overall Judgement:

The relevance of the NMA is insufficient.

Table 2: Credibility of the Evidence-base						
Item	Description	Strength	Weakness	Can't Answer		
				Not Reported	Insufficient Information	Other Reason
1	Did the researchers attempt to identify and include all relevant randomized trials?	Yes	No[A]		X	
2	Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes	No			
3	Is it apparent that poor quality studies were included thereby leading to bias?	No	Yes		X[B]	
4	Is it likely that bias was introduced by selective reporting of outcomes in the studies?	No[C]	Yes		X	
5	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	Yes[D]			
6	If yes (i.e., there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Yes	No			

Notes:

[A] In regard to attempts to identify all relevant randomized trials:

- The complete systematic review was not provided to pCODR but the methods used to search for evidence appeared comprehensive (i.e., information sources, search strategies).

In regard to the inclusion of all relevant randomized trials:

- In the update to the original NMA, the Submitter included a list of all RCTs excluded from the review albeit the reasons used for some exclusions were broad. The NMA included a PRISMA Flow Diagram, however, it is unclear why the total number of unique studies excluded from the NMA changed in the updated NMA compared to the original version since the literature search was not updated.
- pCODR requested that the Submitter *consider* inclusion of PALOMA-2 into the NMA; however, contrary, to what is indicated in the updated NMA report (section 3.1 study selection), pCODR did not request that the data for PALOMA-2 replace the PALOMA-1 data in the primary NMA analysis. Both trials meet the inclusion criteria of the review and should be included. In light of the methodological issues associated with the PALOMA-1 trial it is appropriate to use the results of the blinded independent central review analysis for this trial in the primary NMA analysis opposed to the investigator assessment analysis. The updated NMA includes the PALOMA-1 trial data in sensitivity analyses for the primary endpoint of PFS/TTP and the main analysis for OS, since PALOMA-2 OS data are presently immature.

[B] The level of bias associated with included trials is unclear as the full quality assessment was not included in the submitted NMA. Seven aspects of trial quality were classified as either present, absent or unknown without any judgement statements about the quality of individual trials or the overall quality of the evidence base.

[C] The influence of publication bias was not assessed.

[D] The NMA included seven trials. Among those trials important heterogeneity in patient and study characteristics was noted:

- Three trials included patients who had been previously treated for advanced/metastatic disease with chemotherapy albeit the percentage of these patients was low.
- In four trials not all patients were hormone-receptor positive (range, 45-94%) as a result of some trials including patients with unknown hormone status. A sensitivity analysis was performed excluding the two

trials with <89% of patients who were hormone-receptor positive. The results of this analysis suggested the NMA results were largely unaffected with removal of these trials.
- The HER2 status of included patients was not indicated for a majority of the included trials (five of seven). The proportion of patients HER2- in the other two trials was 94% and 100%.
- Two of the seven trials were open-label, which can introduce bias into the assessment of the primary endpoint (PFS/TTP).
- The definitions of PFS/TTP varied among the trials.

Overall Judgement:
The credibility of the evidence base is judged as a weakness.

Table 3: Credibility of the Analysis							
Item	Description	Strength	Weakness	Can't Answer			
					Not Reported	Insufficient Information	Other Reason
7	Were statistical methods used that preserve within-study randomization? (i.e. no naïve comparisons)	Yes	No → fatal flaw				
8	If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops, was agreement in treatment effects (i.e. consistency) evaluated or discussed?	Yes	No	Not applicable			
9	In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Yes	No	Not applicable			
10	With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias in the analysis?	Yes	No[A]				
11	Was a valid rationale provided for the use of random effects or fixed effects models?	Yes	No				
12	If random effects model was used, were assumptions about heterogeneity explored or discussed?	Yes	No	Not applicable[B]			
13	If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	Yes	No	Not applicable			

Notes:

[A] The NMA included an assessment for imbalance between different types of comparisons in the network of trials; however, it was indicated that the impact of imbalances in treatment effect modifiers (i.e., patient and study characteristics) could not be adjusted for in the analysis due to the presence of several single-study connections between interventions in the networks.

[B] Analyses using both random and fixed effects models were performed; however, results focused on the fixed-effects model.

Overall Judgement:

The credibility of the analysis is judged as a strength.

Table 4: Credibility of Reporting Quality and Transparency						
Item	Description	Strength	Weakness	Can't Answer		
				Not Reported	Insufficient Information	Other Reason
14	Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes	No			
15	Are the individual study results reported?	Yes[A]	No			
16	Are the results of direct comparisons reported separately from results of the indirect comparisons or NMA?	Yes	No			
17	Are all pairwise contrasts between interventions as obtained with the NMA reported along with measures of uncertainty?	Yes	No			
18	Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes	No			
19	Is the impact of important patient characteristics on treatment effects reported?	Yes	No		X[B]	
Notes: [A] The results of individual trials were provided in the form of hazard ratios and confidence intervals but event rates were not reported. [B] The impact of patient characteristics was assessed through sensitivity analyses (i.e., subgroup analysis); however, for some characteristics missing data precluded assessment (i.e., HER2 status) or limited data (and the structure of the evidence network) only permitted a crude assessment (e.g., variations in PFS/TTP endpoints).						
Overall Judgement: The credibility of reporting quality and transparency is judged as a strength.						

Table 5: Credibility of Interpretation						
Item	Description	Strength	Weakness	Can't Answer		
				Not Reported	Insufficient Information	Other Reason
20	Are the conclusions fair and balanced?	Yes	No[A]			

Notes:
[A] In their interpretation of the evidence, the manufacturer indicated the data are limited by heterogeneity and the inability to adjust for its presence within analyses (due to the structure of the evidence network). It was suggested, however, that in most instances the sensitivity analyses performed explained the variation since they yielded similar findings to the primary analysis results. However, the small number of included trials and small sample size, which they also cite as limitations, actually could have compromised the usefulness of sensitivity analyses in identifying any possible differences between various subgroups. Further, their conclusion on the treatment benefit associated with palbociclib-letrozole was not weighted against potential harms.

Overall Judgement:
The credibility of the interpretation is judged as a weakness.

Table 6: Conflict of Interest						
Item	Description	Strength	Weakness	Can't Answer		
				Not Reported	Insufficient Information	Other Reason
20	Were there any potential conflicts of interest?	No	Yes[A]			
21	If yes, were steps taken to address these?	Yes	No[B]			

Notes:
[A] The submitted NMA was funded and performed by employees of the manufacturer and external consultancy groups hired by the manufacturer.
[B] The submitted NMA has not been peer reviewed nor does it address the issue of conflict of interest.

Overall Judgement:
The credibility related to conflict of interest is judged as a weakness.

The overall credibility of the NMA is judged as insufficient.

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