pan-Canadian Oncology Drug Review
Initial Clinical Guidance Report

Palbociclib (Ibrance) for Advanced Breast Cancer

May 5, 2016

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TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the efficacy and safety of palbociclib (Ibrance) in combination with standard endocrine therapy 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).

Palbociclib has a Health Canada approved indication with conditions:

- in combination with letrozole for the treatment of post-menopausal women with ER+, HER2- ABC as initial endocrine-based therapy for their metastatic disease.

Palbociclib has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Palbociclib is an oral capsule available as 75 mg, 100 mg, and 125 mg; it has Health Canada approval in breast cancer for a dose of 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

PALOMA-1 was an international, multicentre, open-label phase 2 randomized controlled trial (RCT) that compared the safety and efficacy of palbociclib plus letrozole (n=84) given orally to letrozole alone (n=81).[1] The trial recruited post-menopausal women (median age of approximately 63 years) with ER+, HER2- ABC who had not received any prior therapies for ABC. Patients were enrolled in two Cohorts simultaneously:

- in Cohort 1, patients were enrolled on the basis of ER+/HER2- biomarker status alone
- in Cohort 2 they were also required to have cancers with amplification of cyclin D1 (CCND1), loss of p16 (INK4A or CDKN2A), or both.

The trial was initially designed as a phase 1/2 trial with the intention of using Cohort 1 as an exploratory analysis of efficacy and safety, while the primary analysis was intended for Cohort 2. The accrual to Cohort 2 was stopped after an unplanned interim analysis of Cohort 1 and the statistical analysis plan for the primary endpoint was amended to a combined analysis of Cohorts 1 and 2 (instead of cohort 2 alone).

Overall, for both Cohorts, patients had visceral involvement and bone metastasis (48% and 18%, respectively). All patients were of ECOG performance status (PS) of 0 and 1 (55% and 45%, respectively). Patients were excluded from trial if they had received letrozole as either neoadjuvant or adjuvant treatment within the 12 months before study entry, had received any previous treatment for ABC, had brain metastasis, or had previously been treated with a CDK inhibitor. This trial also did not permit crossover for patients who had progressed on the letrozole alone arm to the combination of palbociclib plus letrozole.

Over the course of the trial, the protocol was amended a total of eight times. Three amendments involved major changes to the statistical plan, which occurred after

examining the trial data through interim analyses (both unplanned and planned). Changes to the statistical plan included stopping patient enrolment early and combining Cohorts 1 and 2 for efficacy analyses, adding further interim efficacy analyses, and reducing the number of events needed to trigger the final efficacy analysis of the primary outcome (PFS). A substantial number of protocol deviations occurred in the trial (93%) with a higher proportion of these in the palbociclib plus letrozole group (99% vs. 88%).[2] Major protocol deviations occurred much less frequently and were similar between groups (10% for the combination versus 7% for letrozole alone).

Efficacy

The primary endpoint was progression free survival (PFS). Median PFS (mPFS) for combined Cohorts by investigator assessment was 20.2 months (95% CI, 13.8 to 27.5) for the palbociclib plus letrozole group and 10.2 months (95% CI, 5.7 to 12.6) for the letrozole alone group (HR=0.49, 95% CI, 0.32 to 0.75; one-sided p=0.0004). For patients in Cohort 1, mPFS was 26.1 months (95% CI, 11.2 to not estimable [NE]) for the palbociclib plus letrozole group and 5.7 months (95% CI, 2.6 to 10.5) for letrozole alone group (HR=0.30, 95% CI, 0.16 to 0.57; one-sided p<0.0001). For patients in Cohort 2, mPFS was 18.1 months (95% CI, 13.1 to 27.5) for the palbociclib plus letrozole group and 11.1 months (95% CI, 7.1 to 16.4) for the letrozole alone group (HR=0.51, 95% CI, 0.30 to 0.85; one-sided p=0.0046).

The secondary endpoints included overall survival (OS), objective response to treatment, clinical benefit rate, duration of response and safety. At the cut-off date for final analysis (November 29, 2013), there were 19 (23%) of 84 patients in the palbociclib plus letrozole group and eight (10%) of 81 patients in the letrozole alone group remaining on treatment. At the final analysis for PFS, the median OS was 37.5 months (95% CI, 28.4 to NE; 30 events) in the palbociclib plus letrozole group and 33.3 months (95% CI, 26.4 to NE; 31 events) in the letrozole alone group (HR=0.81, 95% CI, 0.49 to 1.35; two-sided p=0.42). The objective response to treatment was higher with combination treatment compared to letrozole alone, both in the intention-to-treat (ITT) population and in the population with measurable disease. Similarly, a greater proportion of patients in the ITT population achieved clinical benefit with combined treatment versus letrozole alone. The median duration of response for patients who had a complete or partial response was 20.3 months for the palbociclib plus letrozole group and 11.1 months for the letrozole alone group.

Harms

The most common serious adverse events (AEs) reported in both treatment groups were neutropenia, leucopenia, and fatigue. Although there were significantly more AEs in the palbociclib plus letrozole group versus letrozole alone (99% versus 84%, respectively), only 13% of patients treated with palbociclib plus letrozole, compared to 2% of patients treated with letrozole alone, discontinued therapy. There were no treatment-related deaths in this trial.

Limitations and Biases

Overall, PALOMA-1 suffered from multiple flaws in design and execution, which makes reaching conclusions about the true benefit of palbociclib-letrozole difficult. 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., 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-letrozole. The multiple data-driven amendment changes compromised the statistical plan of the trial and

cast doubt on the integrity of the obtained results and the magnitude of the reported treatment effect estimates. Although the retrospective BICR of PFS data aligns with the primary analysis, it cannot eliminate all potential bias since treatment decisions were not based on the scanned images used in the BICR.

1.2.2 Additional Evidence

pCODR received input on palbociclib from two patient advocacy groups (ReThink Breast Cancer and Canadian Breast Cancer Network). Provincial Advisory Group input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. One supplemental issue was identified during the development of the review on the critical appraisal of a network meta-analysis provided by the submitter comparing palbociclib plus letrozole with other relevant therapies, including anastrozole, tamoxifen, and exemestane.

1.2.3 Interpretation and Guidance

Breast cancer is a common disease in women. Annually, approximately 25,000 cases (2015 figures) are diagnosed and 5,000 will die, usually after developing metastatic disease.[3] Of these, approximately 65-70% will have ER+ breast cancer and will be treated with targeted agents against estrogen.[4] 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. There is an unmet need to improve PFS in first-line therapy for metastatic breast cancer.

The PALOMA-1 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. 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 groups; however, the trial was not powered to detect a significant difference in OS. Median OS was 37.5 months for palbociclib plus letrozole versus 33.3 months for letrozole alone.

The most common grade 3 or 4 AEs were: neutropenia (54% in the palbociclib plus letrozole group versus 1% 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 and 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 adverse events (e.g., grade 3/4 neutropenia potentially leading to febrile neutropenia) may occur in an unselected non-clinical trial population. The only patient-reported outcome measured was pain, measured using the modified Brief Pain Inventory, to determine if there was a difference in myalgias or arthralgias with the addition of palbociclib to letrozole. There were no measured differences in pain observed between the two groups. There were no reported quality of life parameters in this trial.

To date, data on palbociclib are available from one phase 3 RCT, PALOMA-3, which assessed the clinical benefit of palbociclib in combination with another endocrine therapy, fulvestrant.[5] Palbociclib-fulvestrant was used as second-line therapy for ER+/HER2- post-menopausal ABC patients and therefore does not directly compare to PALOMA-1, but does provide clinical efficacy and safety data for this combination. The results from the intended confirmatory larger phase 3 PALOMA-2 trial reassesses the clinical efficacy and

safety of letrozole in combination with palbociclib versus letrozole alone as first-line endocrine therapy for ER+/HER2- post-menopausal ABC patients, are anticipated in June 2016. Provided the results of PALOMA-2 show similar benefits to PALOMA-1, in the Canadian context, it is likely that the combination of palbociclib and letrozole will replace single-agent first-line endocrine therapy in the metastatic setting. In the interim, based on the results of PALOMA-1, it is possible the use of letrozole in the adjuvant setting for ER+ post-menopausal women may decrease, as prior use of letrozole will be a barrier to receiving the combination of letrozole and palbociclib in the advanced treatment setting.

1.3 Conclusions

The Clinical Guidance Panel concluded that there may be 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-, metastatic breast cancer who have not received any prior treatment for metastatic disease. This was based on the PALOMA-1 clinical trial, which was a small open-label phase 2 RCT. The study demonstrated a statistically significant improvement in PFS. With an absolute improvement in PFS of 10 months, the magnitude of benefit is both statistically and clinically meaningful. There was no significant difference in median OS, but the study was underpowered for this endpoint. 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 and 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., grade 3/4 neutropenia potentially leading to febrile neutropenia) may occur in an unselected non-clinical trial population. The only patient-reported outcome was pain and there was no difference observed between the two groups. There were no reported quality of life parameters in this trial. The Clinical Guidance Panel also considered that from a clinical perspective:

- The Clinical Guidance Panel had concerns about the internal validity and thus quality of the PALOMA-1 trial given that it was a small phase 2 study with many protocol amendments/deviations and skewed population (many de novo metastatic cases).
- The results of PALOMA-2, a large, ongoing, double-blinded phase 3 RCT of palbociclib and letrozole versus letrozole alone for ER+/HER2- ABC as first-line therapy will provide additional data on PFS and OS outcomes, and further information on the safety of this combination therapy. This intended confirmatory trial will provide more robust data and certainty in the magnitude of effect with palbociclib in combination with letrozole compared to letrozole alone, as well as more information about the toxicity profile and use of palbociclib in patients with an ECOG PS of 2. Results are anticipated in June 2016.
- The study design of PALOMA-1 also did not explore the role of combining palbociclib with other endocrine therapies.

2 CLINICAL GUIDANCE

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

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

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

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Advanced or metastatic breast cancer (ABC) is not curative with an expected median life expectancy of approximately 31 months.[6] The goals of systemic therapy consist of improving the overall survival (OS) of these women and to maintain and/or improve their quality of life. Systemic therapy consists of endocrine therapy, targeted therapies and/or cytotoxic chemotherapy. The selection and sequencing of these therapies depend on the biological characteristics of the breast cancer, tumour burden, involvement of vital organs, pace of the disease, performance status, comorbidities of the patient, and patient preference.

The most common type of breast cancer is estrogen receptor positive (ER+) making selective therapies against the estrogen receptor an integral part of systemic therapy in both the adjuvant (curative) and ABC setting. While there is no standard treatment algorithm for ER+ ABC, it is recommended that endocrine therapy be considered the first-line treatment choice unless there is evidence of compromised organ function from metastatic disease. 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) have also demonstrated clinical benefit in post-menopausal advanced endocrine sensitive disease including non-steroidal AIs (letrozole and anastrozole) and steroidal AIs (exemestane). Similarly, fulvestrant, an estrogen receptor downregulator, has shown to be effective in this patient population.

Most estrogen-driven breast cancers will initially respond to endocrine therapy, but this response is limited and the disease eventually becomes resistant to endocrine manipulation and recurs (acquired resistance). There is also a small group of 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 in women whose disease has become resistant to first-line AI therapy.

In addition to the signalling pathways involved in endocrine resistance, it has been well established 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 including the cyclin-dependent kinases (CDKs). Targeting these regulatory proteins and inhibiting their action may provide another therapeutic target to control cell division and inhibit tumour growth. Palbociclib is a reversible, oral, small molecule inhibitor of CDKs 4 and 6 that stops the progression through the cell cycle when partnered with cyclin D. Pre-clinical in vitro studies conducted in tamoxifen-resistant cell lines first demonstrated the synergistic activity of palbociclib in overcoming endocrine resistance when combined with tamoxifen.[7] These findings prompted the PALOMA series of 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+, HER2- ABC.

The potential benefit of combining palbociclib with other endocrine therapy as first-line treatment is the focus of this review.

2.1.2 Objectives and Scope of pCODR Review

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 ER+, HER2- ABC.

Refer to Table 3 in section 6.2.1 for the outcomes and comparators of interest.

2.1.3 Highlights of Evidence in the Systematic Review

One randomized controlled trial (RCT), PALOMA-1, met the inclusion criteria of this systematic review.[1] PALOMA-1 is an ongoing, multicentre, open-label phase 2 RCT comparing palbociclib plus letrozole to letrozole alone as first-line treatment in post-menopausal women with ER+, HER2- ABC.

PALOMA-1 enrolled patients from 50 sites in 12 countries including Canada. Enrolment was conducted using a sequential Cohort design that included two Cohorts of patients. In Cohort 1, patients were enrolled based on ER+ and HER2- status alone. In Cohort 2, patients were also required to have amplification of cyclin D1 (CCND1) and/or loss of p16.

Eligible patients had either locally recurrent disease not amenable to surgery or evidence of metastatic or bone-only disease and ECOG performance status of 0 or 1. Previous treatment for advanced or metastatic disease and any previous treatment with letrozole (within 12 months of the start of the trial) or a CDK inhibitor were prohibited. Randomization was stratified by disease site and disease-free interval (≤ 12 versus >12 months from the end of adjuvant treatment to recurrence or de novo metastatic disease). Pfizer funded the trial and their staff were involved in all aspects its conduct, including study design, treatment administration, data collection and interpretation, and final publication. Refer to section 6.3.2 for a more detailed description of the PALOMA-1 trial. Table 2 addresses the generalizability of the evidence from the trial.

The primary outcome of the trial was investigator assessed progression-free survival (PFS). Secondary outcomes included objective response rate (ORR), clinical benefit (defined as

the sum of complete and partial responses and stable disease for 24 or more weeks), duration of response, OS, patient-reported pain, and safety.

The trial was initially designed as a phase 1/2 trial with the intention of using Cohort 1 as an exploratory analysis of efficacy and safety, while the primary analysis was intended for Cohort 2. The original sample size calculation of 150 patients was based on Cohort 2 only. Over the course of the trial, however, the protocol was amended a total of eight times. Three amendments involved major changes to the statistical plan, which occurred after examining the trial data through interim analyses (both unplanned and planned). Changes to the statistical plan included stopping patient enrolment early and combining Cohorts 1 and 2 for efficacy analyses, adding further interim efficacy analyses, and reducing the number of events needed to trigger the final efficacy analysis of the primary outcome (PFS). Patient enrolment was stopped after 165 patients had been randomized (66 in Cohort 1 and 99 in Cohort 2). The final analysis of PFS was conducted according to intent-to-treat (ITT) with adjustment of the statistical significance level to account for the interim analyses. For a more detailed explanation of the statistical amendment changes refer to section 6.3.2.1.

Due to the number of data-driven amendment changes, as well as the open-label design and small sample size of the trial, the FDA requested the trial sponsor conduct a blinded independent central review (BICR) of the PFS data. The BICR analysis was carried out retrospectively and was considered a secondary outcome.

In the Combined Cohort (n=165), 84 patients were randomized to palbociclib-letrozole and 81 were randomized to letrozole alone. The treatment groups were generally well balanced with respect to baseline characteristics except for slight imbalances in disease site, disease-free interval, and previous treatment. The median age of patients was 63 years. The majority of patients were white (90%) with ECOG status of 0 (55%). Almost all patients presented with stage IV disease (98%). A large proportion of patients had not received any prior systemic therapy, with 49% of patients presenting with de novo advanced/metastatic disease. Among patients previously treated in the adjuvant setting, 43% had received chemotherapy and 33% had received hormone therapy. Canadian patients comprised 3% of the trial population.

All patients in PALOMA-1 received letrozole at a continuous dose of 2.5 mg once daily. Patients in the experimental group also received palbociclib at a dose of 125 mg once a day for three weeks followed by one week off in a 28-day cycle. Treatment was continued until disease progression, unacceptable toxicity, study withdrawal or death. At the final data analysis, 76% of patients receiving palbociclib-letrozole and 85% receiving letrozole alone had discontinued treatment. In both groups the primary reason for discontinuation was disease progression. The post-progression treatment received by patients was not reported.

A substantial number of protocol deviations occurred in the trial (93%) with a higher proportion of these in the palbociclib plus letrozole group (99% vs. 88%).[2] Major protocol deviations occurred much less frequently and were similar between groups (10% for the combination versus 7% for letrozole alone). An FDA review, which included post-hoc analyses of trial data, concluded the deviations did not impact the overall efficacy results.[2,8,9]

The key efficacy data from PALOMA-1 is summarized in Table 1. After a median follow-up of approximately 30 months, 41 PFS events had occurred in the palbociclib-letrozole group compared to 59 in the letrozole alone group. Median PFS time was approximately doubled in patients receiving palbociclib-letrozole compared to letrozole alone (20.2 months versus

10.2 months; one-sided p=0.0004). The PFS benefit was consistent across all patient subgroups examined with the exception of those with disease recurrence within ≤12 months of the end of adjuvant therapy (excluding patients with de novo disease).

The results of the BICR analysis confirmed the investigator assessment but the treatment effect was of lower magnitude (Table 1). This difference in result was explored through multiple post-hoc analyses, which identified censoring rates (arising from differences in the determination of progression in bone only disease) and investigator bias (imbalance in cases where the investigator assessment determined stable disease in the palbociclib-letrozole group while the BICR analysis determined disease progression) as contributing factors.[2,8]

All secondary outcomes, including ORR, duration of response, and clinical benefit, favoured palbociclib-letrozole (Table 1). Overall survival data were immature at the time of the final analysis of PFS data and showed no significant difference between groups. It should be noted that the trial was not powered for an OS comparison. The addition of palbociclib to letrozole did not appear to affect pain outcomes as measured by both pain severity and pain interference scales of the modified Brief Pain Inventory short-form.

Adverse events that occurred more frequently with palbociclib-combined treatment included neutropenia (74% versus 5%), leucopenia (43% versus 3%), fatigue (41% versus 23%), anemia (35% versus 6%), nausea (25% versus 13%) and alopecia (22% versus 3%). The majority of these were low-grade with the exception of neutropenia (grade 3-4, 54% versus 1%). Serious adverse events were reported at 8% in the palbociclib-letrozole group and included pulmonary embolism, back pain and diarrhea. Adverse events led to a delay in the start of treatment in 45%, dose reductions in 40%, and treatment discontinuation in 13% of patients in the palbociclib-letrozole group. No treatment-related deaths were reported.

The limitations and risk of bias associated with the PALOMA-1 trial are fully discussed in section 6.3.2.1. Overall, PALOMA-1 suffered from multiple flaws in design and execution, which makes reaching conclusions about the true benefit of palbociclib-letrozole difficult. 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., 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-letrozole. The multiple data-driven amendment changes compromised the statistical plan of the trial and cast doubt on the integrity of the obtained results and the magnitude of the reported treatment effect estimates. Although the retrospective BICR of PFS data aligns with the primary analysis, it cannot eliminate all potential bias since treatment decisions were not based on the scanned images used in the BICR.

Table 1: Key Efficacy Outcomes in the PALOMA-1 trial (Combined Cohort ITT Population).[1]		
Treatment Groups	**Palbociclib + Letrozole**	**Letrozole alone**
Median follow-up, months	29.6	27.9
No. patients remaining on treatment, n (%)	19 (23)	8 (10)
Primary Outcome - Investigator Assessed PFS[A]	n=84	n=81
No. PFS events (%)	41(48.8)	59 (72.8)
Median PFS, months (95% CI)	20.2 (13.8-27.5)	10.2 (5.7-12.6)
Hazard ratio (95% CI; one-sided p-value)	0.49 (0.32-0.75; p=0.0004)	
Secondary Outcome - BICR-assessed PFS[A,H]	n=84	n=81
No. PFS events (%)	31(36.9)	33 (40.7)
Median PFS, months (95% CI)	25.7 (17.7-NR)	14.8 (9.3-20.4)
Hazard ratio (95% CI; one-sided p-value)	0.62 (0.38-1.02; p=0.03)	
Other Key Secondary Outcomes	n=84	n=81
Objective Response Rate[B] % (95% CI)	43(32-54)	33 (23-45)
One-sided p-value	p=0.13	
Duration of Response[C]		
Median duration in months (95% CI)	20.3 (13.4-25.8)	11.1 (9.3-31.6)
One-sided p-value	p=NR	
Clinical Benefit[D]		
No. (%) patients achieving clinical benefit (%)	68 (81)	47 (58)
One-sided p-value	p=0.0009	
Overall Survival		
No. deaths	30	31
Median, months (95% CI)	37.5 (28.4-NE)	33.3 (26.4-NE)
Hazard ratio (95% CI; two-sided p-value)	0.81 (0.49-1.35; p=0.42)	
Patient-reported Pain[E,I]	n=76	n=74
Pain Severity Scale, mean change from baseline (SE)	0.4 (0.29)	0.2 (0.32)
Mean Difference (95% CI), p-value	0.2 (-0.7-1.0), p=0.69	
Pain Interference Scale, mean change from baseline (SE)	0.8 (0.34)	0.4 (0.30)
Mean Difference (95% CI), p-value	0.4 (-0.5-1.3), p=0.33	
Harms Outcomes	n=83	n=77
Any grade adverse event, n (%)	82 (99)	65 (84)
Grade 3-4 adverse event, n (%)	63 (76)	16 (21)
Any serious adverse event, n (%)	7 (8)	5 (6)
Adverse event leading to treatment discontinuation, n (%)	11 (13)[F]	2 (3)[G]

Abbreviations: **BICR** - blinded independent central review; **CI** - confidence interval; **ITT** - intent-to-treat; **No./n** = number; **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] As measured by the Modified Brief Pain Inventory-Short Form Pain Severity and Pain Interference Scales.

[F] Of these patients, six (7%) discontinued due to a treatment-related adverse event.

[G] The two patients (2%) discontinued due to a treatment-related adverse event.

[H] Source: FDA Medical Review and Evaluation Report[2]

[I] Source: ClinicalTrials.gov clinical trial record[10]

2.1.4 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.

2.1.5 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+ and HER2- ABC,[11] was summarized and critically appraised using the ISPOR Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire. The NMA found a statistically significant difference in PFS (or time-to-progression) in favour of palbociclib-letrozole relative to letrozole, anastrozole, and exemestane. All sensitivity analyses performed indicated the PFS results were robust to differences in the patient or study characteristics assessed. No differences in OS were demonstrated. 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 analysis (versus only single-agent regimens) as well as other outcomes (adverse events, quality of life) and significant heterogeneity across included trials. The conclusions drawn from the NMA should be interpreted with caution.

See section 7.1 for more information.

2.1.6 Other Considerations

See section 4 and section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) input, respectively.

Patient Advocacy Group Input

Two patient advocacy groups, Rethink Breast Cancer (Rethink) and Canadian Breast Cancer Network (CBCN), provided input on the palbociclib (Ibrance) submission as treatment for HER2- ABC as initial endocrine-based therapy, and their input is summarized below.

From a patient's perspective, managing a diagnosis of metastatic breast cancer is a challenge, as current treatment options 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 ABC represent a significant or debilitating impact (both physical and social) on the 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, most respondents were able to tolerate these side effects, while others had to reduce their dosage of palbociclib. Respondents were also asked about

the impact of drug administration, and commented on the ease of the oral dosage and appreciated having a break of one week on the treatment.

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:
- Indication creep to patients previously treated for metastatic disease
- Monthly monitoring and blood work for neutropenia

Economic factors:
- Large number of patients
- High cost of drug relative to currently available oral treatments

Other

The product monograph provided by the manufacturer identified serious warnings and precautions, specifically, neutropenia as a significant adverse drug reaction identified in clinical trials conducted with palbociclib.

2.2 Interpretation and Guidance

Breast cancer is a common disease in women. Annually, approximately 25,000 cases (2015 figures) are diagnosed and 5,000 will die, usually after developing metastatic disease.[3] Of these, approximately 65-70% will have estrogen responsive positive (ER+) breast cancer and will be treated with targeted agents against estrogen.[4] 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. There is an unmet need to always improve PFS in first-line therapy for metastatic breast cancer.

The PALOMA-1 clinical trial 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.[1] This was an international trial study 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 groups; however, the trial was not powered to detect a significant difference in OS. Median OS was 37.5 months for palbociclib plus letrozole versus 33.3 months for letrozole alone (HR=0.81; 95% CI, 0.49 to 1.35; two-sided p=0.42).

The most common grade 3 or 4 AEs were: neutropenia (54% in the palbociclib plus letrozole group versus 1% 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 and 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 adverse events (e.g., febrile neutropenia) may occur in an unselected non-clinical trial population. The only patient-reported outcome measured was pain, measured using the modified Brief Pain Inventory, to determine if there was a difference in myalgias or arthralgias with the addition of palbociclib to letrozole. There were no measured differences in pain observed between the two groups. There were no reported quality of life parameters in this trial.

To date, data on palbociclib are available from one phase 3 RCT, PALOMA-3, which assessed the clinical benefit of palbociclib in combination with another endocrine therapy, fulvestrant.[5] Palbociclib-fulvestrant was used as second-line therapy for ER+/HER2- post-menopausal ABC patient and therefore does not directly compare to PALOMA-1, but does provide clinical efficacy and safety data for this combination. The results from the intended confirmatory larger phase 3 PALOMA-2 trial reassesses the clinical efficacy and safety of letrozole in combination with palbociclib versus letrozole alone as first-line endocrine therapy for ER+/HER2- post-menopausal ABC patients, are anticipated in June 2016. Provided the results of PALOMA-2 show similar benefits to PALOMA-1, in the Canadian context, it is likely that the combination of palbociclib and letrozole will replace single agent first-line endocrine therapy in the metastatic setting. In the interim, based on the results of PALOMA-1, it is possible the use of letrozole in the adjuvant setting for ER+ post-menopausal women may decrease, as prior use of letrozole will be a barrier to receiving the combination of letrozole and palbociclib in the advanced treatment setting.

The assessment of generalizability of evidence is limited to the patient population studied and evidence from PALOMA-1. Refer to Section 6.3.2.1 e) Limitations/Biases for details on identified limitations and biases associated with the trial.

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 (PALOMA-1) 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%)	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. PALOMA-2 will provide further information on patients with an ECOG PS of 2.
	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%)	Is this representative of how patients present in Canadian practice? Does this limit the interpretation of the trial results to stage IV patients?	Interpretation of the trial results applies to metastatic disease (stage IV).

Domain	Factor	Evidence (PALOMA-1) and PAG input	Generalizability Question	CGP Assessment of Generalizability
	Brain metastases	PALOMA-1: patients with brain metastases 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.
	Time since progression (disease-free interval)	PALOMA-1: a statistically significant treatment effect in PFS was observed in favour of the palbociclib plus 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 examined (n=29; HR=0.77, 95% CI, 0.23-2.5). [A]	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?	The subgroup is too small to assess the validity of the finding.
	De novo disease	PALOMA-1: 49% 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.
Comparator	Standard of care: other endocrine therapy	PAG noted that various AIs are available for initial treatment in ER-+/HER2- disease, including anastrozole, exemestane and letrozole. PALOMA-1 compares palbociclib plus letrozole to letrozole alone.	Are the findings of this trial limited to letrozole, or are they generalizable to other AIs? Why or why not?	Although the CGP were of the opinion that the three available AIs have similar activity, direct comparisons and toxicity data for other combinations are lacking.

Domain	Factor	Evidence (PALOMA-1) and PAG input	Generalizability Question	CGP Assessment of Generalizability
		A submitted network meta-analysis found a statistically significant difference in PFS (or time-to-progression) in favour of palbociclib-letrozole relative to letrozole, anastrozole, and exemestane. No differences in OS were demonstrated. 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 analysis (versus only single-agent regimens) as well as other outcomes (adverse events, quality of life) and significant heterogeneity across included trials. The conclusions drawn from the NMA should be interpreted with caution.		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 plus letrozole compared to other endocrine therapies was better given the overall flaws in PALOMA-1 and the exclusion of relevant studies in the network meta-analysis. However, it is likely a combination therapy is better than single agent therapy.
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 arms, respectively (median: 37.5 months vs. 33.3 months; HR=0.81, 95% CI, 0.49-1.35; p=0.42).	Is OS at just over two years reflective of longer-term survival? Why or why not?	The trial was too small to detect any meaningful OS results. However, there was a trend to improvement in median OS in the combination group. PALOMA-2 will provide further efficacy results for median OS.

Domain	Factor	Evidence (PALOMA-1) and PAG input	Generalizability Question	CGP Assessment of Generalizability
Setting	Study Centres	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%)	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 must underlie the high number of de novo metastatic cases included.
Abbreviations: **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; **PAG** - Provincial Advisory Group; **PFS** - progression-free survival; **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.				

2.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit to the combination of palbociclib and letrozole compared with letrozole alone in the treatment of post-menopausal women with ER+, HER2-, ABC who have not received any prior treatment for metastatic disease. This was based on the PALOMA-1 clinical trial, which was a small open-label phase 2 RCT. The study demonstrated a statistically significant improvement in PFS. With an absolute improvement in PFS of 10 months, the magnitude of benefit is both statistically and clinically meaningful. There was no significant difference in median OS, but the trial was underpowered for this endpoint. 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 and 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, there was no difference observed between the two groups. There were no reported quality of life parameters in this study. The Clinical Guidance Panel also considered that from a clinical perspective:

- The Clinical Guidance Panel had concerns about the internal validity and thus quality of the PALOMA-1 trial given that it was a small phase 2 study with many protocol amendments/deviations and skewed population (many de novo metastatic cases).
- The results of PALOMA-2, a large, ongoing, double-blinded phase 3 RCT of palbociclib and letrozole versus letrozole alone for ER+/HER2- ABC as first-line therapy will provide additional data on PFS and OS outcomes, and further information on the safety of this combination therapy. This intended confirmatory trial will provide more robust data and certainty in the magnitude of effect with palbociclib in combination with letrozole compared to letrozole alone, as well as more information about the toxicity profile and use of palbociclib in patients with an ECOG PS of 2. Results are anticipated in June 2016.
- The study design of PALOMA-1 also did not explore the role of combining palbociclib with other endocrine therapies.

3 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.

3.1 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.[3] 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.[6]

The goals of systemic therapy in ABC consist of improving overall survival (OS) and or/ progression free survival (PFS) of these women 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+).[4] 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 downregulator, 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.

3.2 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.[7]

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.

3.3 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. This would include post-menopausal women with ER+, HER2- ABC that 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. Further data will be available in terms of post-progression therapy when the larger, double-blind phase 3 PALOMA-2 trial is reported, which will provide further guidance into the sequencing of endocrine therapy in clinical practice.

3.4 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).[5]

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 trial population). Further studies are warranted in these patient populations.

4 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) submission as treatment for estrogen receptor positive (ER+) human epidermal growth factor negative (HER2-) advanced breast cancer (ABC) as initial endocrine-based therapy, and their input is summarized below.

CBCN in collaboration with Rethink conducted an online survey of ABC 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.

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.

Rethink 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.

CBCN and Rethink also reviewed additional print sources, including current studies and grey literature and sought advice from Rethink's breast cancer scientific advisory committee to identify issues and experiences that are commonly shared among many women living with breast cancer in order to provide supporting context.

From a patient's perspective, managing a diagnosis of ABC is a challenge, as current treatment options 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 ABC represent a significant or debilitating impact (both physical and social) on the 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, most respondents were able to tolerate these side effects, while others had to reduce their dosage of palbociclib. Respondents were also asked about the impact of drug administration, and 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.

4.1 Condition and Current Therapy Information

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

According to Rethink and CBCN, current treatment options for ER+ ABC 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 ABC 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 ABC, as well as the treatments that are used, impact both the social and physical well-being of a patient. 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 ABC 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. The key responses reported by respondents were:

- 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

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 ABC 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.

4.1.2 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 ABC 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.

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

One respondent stated: "*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*."

According to the responses from key informant interviews conducted by CBCN, it was submitted that women with ER+ 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."*

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.

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."*

4.1.3 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 ABC.

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 ABC, 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."*

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Palbociclib

According to CBCN and Rethink, 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 the quality of life. CBCN and Rethink submitted that when living with no or with minimal cancer-related symptoms, and with minimal side effects from the treatment, patients are able to reduce the impact of cancer on their ability to care for children and dependents, continue with their employment and earn income, spend time with loved ones and participate in their life in a meaningful way by engaging in social activities, travelling, maintaining friendships, and pursuing personal interests.

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 the 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 that 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, and Patient 3 expressed that she was very fortunate to be have experienced only minimal side effects on the treatment. 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*. " –Patient 3

When respondents were asked about adverse effects and symptoms, CBCN reported that respondents identified febrile neutropenia and fatigue as side effects of the treatment, but all three respondents indicated that the side effects were very manageable through dosage adjustments and support medications.

The following responses 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.* "

Rethink noted that because this indication is in the first-line of care for ER positive, HER2 negative ABC 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. Overall the

respondents that Rethink had interviewed stated that this therapy is much easier than others including traditional chemotherapy.

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*."

4.3 Additional Information

No additional information.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

Input was obtained from 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:

- Indication creep to patients previously treated for metastatic disease
- Monthly monitoring and blood work for neutropenia

Economic factors:

- Large number of patients
- High cost of drug relative to currently available oral treatments

Please see below for more details.

5.1 Factors Related to Comparators

Various aromatase inhibitors are available for initial treatment of metastatic disease in estrogen-receptor positive (ER+), human epidermal growth factor receptor negative (HER2) breast cancer. These include anastrozole, exemestane and letrozole. PAG noted that the PALOMA-1 trial compares palbociclib plus letrozole to letrozole alone and is seeking comparative data to other aromatase inhibitors.

PAG noted that the results of the PALOMA-3 trial for palbociclib in combination with fulvestrant were published in 2015 and there may be clinician interest in using this combination. However, PAG noted that fulvestrant is not currently funded in any provinces.

5.2 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.

5.3 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.

5.4 Factors Related to Implementation Costs

As palbociclib is administered orally, chemotherapy units and chair time would not be required.

The availability of three different strengths facilitates dose adjustments as the tablet strengths correlate with the dose adjustments. These are enablers to implementation.

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.

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 blood work.

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 drug compared to letrozole alone and other oral therapies.

5.5 Factors Related to Health System

PAG noted that palbociclib is an oral drug that 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.

5.6 Factors Related to Manufacturer

The high cost and large potential budget impact of palbociclib is a barrier to implementation. 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.

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
Randomized controlled trials	• 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)	Endrocrine 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.

**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.*

6.2.2 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 (1974-) via Ovid; The Cochrane Central Register of Controlled Trials via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was 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 April 7, 2016.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium (SABCS) 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 additional information as required by the pCODR Review Team.

6.2.3 Study Selection

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

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

6.2.4 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. Another member of the pCODR Review Team performed an audit of all extracted data.

6.2.5 Data Analysis

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

6.2.6 Writing of the Review Report

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

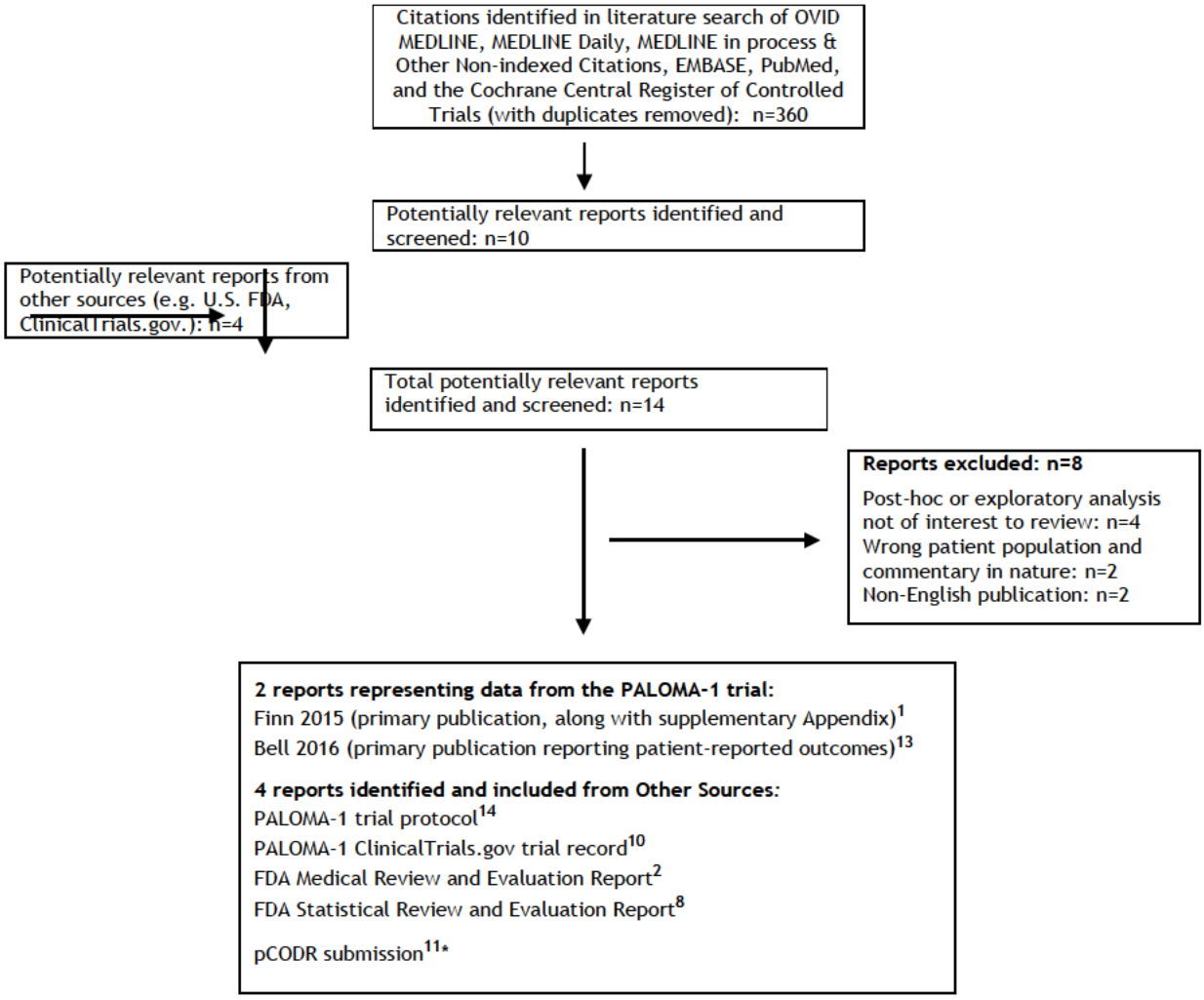
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions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

6.3 Results

6.3.1 Literature Search Results

Of the potentially relevant reports identified for full text review (n=14), six reports were included in the pCODR systematic review[1,2,8,10,13,14] and eight 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,[15-18] they were the wrong patient population and also commentary in nature,[19,20] or were only published in a language other than English.[21,22]

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



**Note: Additional data related to the PALOMA-1 trial were also obtained through requests to the Submitter by pCODR.*

6.3.2 Summary of Included Studies

One randomized controlled trial (RCT) was identified that met the eligibility criteria of this review. The key characteristics of this trial are summarized in Table 4 and specific aspects of trial quality are summarized in Table 5.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of key trial characteristics of the included PALOMA-1 trial comparing palbociclib combined with letrozole as first-line treatment in post-menopausal women with ER-positive and HER2-negative advanced or metastatic breast cancer.

PALOMA-1[1]				
Trial Design	**Eligibility Criteria**	**Intervention**	**Comparator**	**Outcomes**
Clinical Trial NCT00721409 Open label phase 2 RCT Patient enrolment: December 2009 to May 2012 Data cut-off date: November 29, 2013 N randomized = 165 Multicentre (50 sites in 12 countries) Randomized 1:1 ratio, 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* • Cohort 1 (ER-positive and HER2-negative status) • Cohort 2 (CCND1 amplification, loss of p16 or both) Funded by Pfizer	<u>Key Inclusion Criteria:</u> • Age ≥ 18 years • ER-positive • Locally recurrent disease not amenable to surgery 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	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, unacceptable toxicity, study withdrawal or death.	Letrozole alone (oral 2.5 mg once daily)	<u>Primary</u>: • Progression-free survival (investigator assessed) <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; **HER2**- human epidermal growth factor receptor 2; **PR** - partial response; **RCT** - randomized control trial; **RECIST** - Response Evaluation Criteria in Solid Tumors.

Notes:
*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.

Table 5: Select quality features of the included PALOMA-1 trial comparing palbociclib combined with letrozole versus letrozole alone 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 [A]	Sample Size	Randomization Method	Allocation Concealment	Blinding	ITT analysis	Final Analysis	Early Termination	Ethics Approval
PALOMA-1[1]	Palbociclib + letrozole vs. letrozole alone	Investigator assessed PFS	*Initial:*[B] 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:*[C] 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:*[D] 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[E] using block size of 6	No	No[F]	Yes	Yes[G]	No	Yes

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

Notes:
[A] 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).
[B] 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.

[C] 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.
[D] 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.
[E] Randomization was stratified for disease site, disease-free interval, and study Cohort.
[F] 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.
[G] 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

One RCT, PALOMA-1, met the inclusion criteria of this systematic review.[1] PALOMA-1 is an ongoing phase 2 trial comparing combination treatment with palbociclib and letrozole to letrozole alone as first-line treatment in post-menopausal women with ER+, HER2- ABC.

PALOMA-1 is an international, open-label, multi-centre trial that 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).

Trial eligibility criteria required that patients have either locally recurrent disease not amenable to surgery or evidence of metastatic or bone-only disease measurable by RECIST criteria. Previous treatment for ABC, and any previous treatment with letrozole (within 12 months of the start of the trial) or a CDK inhibitor, was prohibited. The trial included patients with an ECOG performance status of 0 or 1 and specifically excluded patients with brain metastases.

Patients were randomized in a 1:1 ratio to treatment groups using a centralized interactive web-based randomization system. 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) and carried out using a block size of 6.

The primary outcome of the trial was investigator assessed progression-free survival (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:

- Objective response rate (ORR)
- Clinical benefit (defined as the sum of complete plus partial responses and stable disease for 24 or more weeks)
- Duration of response
- Overall survival (OS)
- Patient-reported outcomes that included an assessment of pain severity and pain interference as measured by the modified Brief Pain Inventory short-form (BPI-sf), and
- Safety

The trial protocol was amended eight times over the course of the trial. Three amendments involved major changes to the statistical plan of the trial, 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 (biomarker-unselected group) as an exploratory analysis of efficacy and safety, while the primary analysis of efficacy and safety was intended for Cohort 2 (biomarker-selected patients). 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 statistical plan was amended to analyze the primary endpoint in Cohorts 1 and 2 combined. The authors report that this amendment was made prospectively 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.[8] After the second interim analysis was conducted, a substantial fall in event rates (observed over an unspecified amount of time) prompted another amendment to the statistical plan. 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 intent-to-treat (ITT) with adjustment of the statistical significance level to account for the interim analyses. A hierarchal gate-keeping procedure was used for hypothesis testing in order to control the type I error rate for multiple comparisons. Such 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% confidence intervals 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 blinded independent central review (BICR) of the PFS data.[8] The BICR analysis 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) and included the following:

- 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

The statistical methods used to compare differences between groups in the secondary outcomes of interest were not reported in the primary trial publication. However, statistical comparisons were reported for clinical benefit and adverse events (AEs) but the methods used to attain significance values were not reported. 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.[8]

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

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-1 trial are summarized in Table 6.

For the Combined Cohorts, a total of 165 patients were randomly assigned in PALOMA-1 (ITT population); 84 and 81 were randomized to palbociclib-letrozole and letrozole alone, respectively. The authors reported that treatment groups were generally well balanced with respect to baseline patient demographic and prognostic variables except for slight imbalances in 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.[8]

The median age of patients was approximately 63 years, with almost all patients presenting with stage IV disease (98%, n=162). The majority of patients were white[2] (90%, n=148) and had an ECOG status of 0 (55%, n=91). Site of disease was categorized as visceral, bone only, or other in 48% (n=80), 18% (n=29), and 34% (n=56) of patients, respectively. A large proportion of patients had not received any prior systemic therapy, with 49% (n=81) of patients presenting with de novo advanced disease. Among patients previously treated in the adjuvant setting, 43% (n=71) had received chemotherapy and 33% (n=55) had received hormone therapy. Of the patients treated with hormone therapy, 29% (n=48) were treated with tamoxifen and 17% (n=28) were treated with aromatase inhibitors. 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

All patients in the PALOMA-1 trial received a continuous regimen of letrozole at a dose of 2.5 mg once daily. Patients allocated to the combination group also received palbociclib at a dose of 125 mg once a day for three weeks followed by one week off in a 28-day cycle. Treatment was continued until disease progression, unacceptable toxicity, study withdrawal or death. Dose modifications were permitted in the trial, with dose reduction guidelines outlined for management of specific toxicities as well as criteria for resuming treatment.

Limited information on treatment exposure for patients receiving palbociclib was provided in the primary trial publication. The FDA Medical Review Report provided a more comprehensive summary of these data.[2] The median daily dose of palbociclib was 125 mg (range, 79.6-266.7 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-1 trial is provided in Table 7. At the final data analysis, 76% (n=64) of patients in the palbociclib-letrozole group and 85% (n=69) 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% (n=19) in the palbociclib-letrozole group and 10% (n=8) 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 primary PALOMA-1 publication. However, the FDA Medical Review Report,[2] 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 the following:

- Multiple patients being stratified incorrectly at randomization (stratification performed was different from what was recorded on case report forms, which was deemed accurate)
- Assessments performed outside of the allowed time window (typically two or three weeks outside of window but subsequent assessments were without progression)
- 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.[2,8]

Table 6: Baseline patient characteristics in the PALOMA-1 trial.[1]						
	Combined Cohort ITT analysis population (n=165)		Patient Cohort 1 (n=66)		Patient Cohort 2 (n=99)	
Treatment Groups	Palbociclib + letrozole	Letrozole alone	Palbociclib + letrozole	Letrozole alone	Palbociclib + letrozole	Letrozole alone
No. patients randomized	**84**	**81**	**34**	**32**	**50**	**49**
Baseline patient characteristics, n (%) unless otherwise specified						
Median age, years (range)	63 (41-89)	64 (38-84)	66 (41-89)	64 (42-75)	62 (46-83)	63 (38-84)
ECOG status:						
0	46 (55)	45 (56)	23 (68)	20 (63)	23 (46)	25 (51)
1	38 (45)	36 (44)	11 (32)	12 (38)	27 (54)	24 (49)
Disease stage:						
III	2 (2)	1 (1)	2 (6)	0	0	1 (2)
IV	82 (98)	80 (99)	32 (94)	32 (100)	50 (100)	48 (98)
Disease site:*						
Visceral	37 (44)	43 (53)	10 (29)	11 (34)	27 (54)	32 (65)
Bone	17 (20)	12 (15)	7 (21)	6 (19)	10 (20)	6 (12)
Other (non-visceral)	30 (36)	26 (32)	17 (50)	15 (47)	13 (26)	11 (23)
Disease-free interval:*						
>12 months from adjuvant treatment to recurrence	25 (30)	30 (37)	10 (29)	10 (31)	15 (30)	20 (41)
≤ 12 months from adjuvant treatment to recurrence or de-novo advanced disease	59 (70)	51 (63)	24 (71)	22 (69)	35 (70)	29 (59)
De novo advanced disease only	44 (52)	37 (46)	19 (56)	17 (53)	25 (50)	20 (41)
Previous systemic therapy:						
None	44 (52)	37 (46)	19 (56)	17 (53)	25 (50)	20 (41)
Chemotherapy	34 (40)	37 (46)	11 (32)	14 (44)	23 (46)	23 (47)
Hormonal:	27 (32)	28 (35)	11 (32)	11 (34)	16 (32)	17 (35)
Tamoxifen	24 (29)	24 (30)	8 (24)	8 (25)	16 (32)	16 (33)
Anastrozole	8 (10)	11 (14)	4 (12)	5 (16)	4 (8)	6 (12)
Letrozole	2 (2)	1 (1)	0	0	2 (4)	1 (2)
Exemestane	4 (5)	2 (2)	3 (9)	1 (3)	1 (2)	1 (2)
Abbreviations: ECOG - Easter Cooperative Oncology Group; ITT - intent-to-treat; No./n - number.						
Notes: ***Based on case report form data.**						

Table 7: Patient disposition in the PALOMA-1 trial.[1]						
	Combined Cohorts (n=165)		Cohort 1 (n=66)		Cohort 2 (n=99)	
Treatment arms, n (%)	Palbociclib + letrozole	Letrozole alone	Palbociclib + letrozole	Letrozole alone	Palbociclib + letrozole	Letrozole alone
Patients randomized	**84**	**81**	**34**	**32**	**50**	**49**
Received allocated treatment	83 (99)	77 (95)	33 (97)	29 (91)	50 (100)	48 (98)
Did not receive allocated treatment	1 (1)	4 (5)	1 (3)	3 (9)	0	1 (2)
Withdrew consent	1 (1)	4 (5)	1 (3)	3 (9)	0	1 (2)
Patients continuing randomized treatment	19 (23)*	8 (10)*	NR	NR	NR	NR
Patients discontinuing randomized treatment	64 (76)	69 (85)	26 (76)	28 (88)	38 (76)	41 (84)
Primary reasons for discontinuation:						
Adverse events	11 (13)	2 (2)	8 (24)	1 (3)	3 (6)	1 (2)
Objective progression or relapse	42 (50)	57 (70)	16 (47)	22 (69)	26 (52)	35 (71)
Deterioration of health status	5 (6)	3 (4)	0	1 (3)	5 (10)	2 (4)
Death	1 (1)	0	0	0	1 (2)	0
Withdrew consent	5 (6)	5 (6)	2 (6)	2 (6)	3 (6)	3 (6)
Other	0	2 (2)	0	2 (6)	0	0
Protocol deviations:						
Any deviation**	83 (99)	71 (88)	33 (97)	28 (88)	50 (100)	43 (88)
Major deviation***	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.[2]
*** Includes any significant deviation related to: inclusion/exclusion criteria, investigational product, procedure/tests, and randomization.[2]

e) Limitations/Sources of Bias

Refer to Table 5 for a summary of key quality-related features of the PALOMA-1 trial.

Overall, the PALOMA-1 trial 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 vs. progressive disease status in the experimental arm.
- In total, there were eight amendments made to the trial protocol; three of these were data driven, and included changes to the statistical analysis plan. Such changes compromised the statistical plan 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.[9] Further, all these changes raise the question of how many times the 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%; n=153). 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 quality of life 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 as well as failure to adjust for multiple comparisons and the concomitant use of pain medications.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

A summary of the key efficacy results from the PALOMA-1 trial can be found in Table 8.

Primary Outcome

Investigator-Assessed Progression-free Survival

The data cut-off date for the final analysis was November 29, 2013.[1] 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 (approximately doubled) 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. The median improvement in PFS (over letrozole alone) was 7.0 months in Cohort 2 compared to 20.4 months in Cohort 1.

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.[2]

Key Secondary Outcomes

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

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.[2] 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. It was noted that the missing data (i.e., four patients) were evenly distributed among the trial arms. In contrast to the investigator assessment, the BICR assessment was only stratified by Cohort.

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 Cohorts, no difference in PFS was observed in Cohort 1, and in Cohort 2, median PFS was improved by approximately six months in the combined treatment group. The treatment effect observed in Cohort 2 was of greater magnitude compared to the result obtained for the Combined Cohort analysis (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 (arising from determination of progression in bone only disease, which was acknowledged as being difficult to assess using RECIST criteria) 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). While a sensitivity analysis performed after a review of the individual CRF of all discrepant cases showed results consistent with the investigator assessment of PFS; it was noted that the influence of investigator bias could not entirely be eliminated.

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

Objective response rate as measured by the investigator and defined as the sum of complete and partial responses, 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

The duration of response, defined as the duration of complete or partial 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 provided.

Clinical Benefit

Clinical benefit, defined as the sum of complete plus partial responses and stable disease for a period of ≥ 24 weeks, 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

Overall survival data were deemed immature at the time of the final analysis of PFS data. 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).

Modified Brief Pain Inventory (mBPI-sf)

Patient-reported pain, including assessment of pain severity and its interference with daily activities, was measured in the PALOMA-1 trial using the mBPI-sf. The 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.[13] The trial record for PALOMA-1 on the clinicaltrials.gov website also provides additional summary data for the Combined and individual Cohorts.[10] The results are provided in Table 9. 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.[13] 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.[13] 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.[13] Overall, the addition of palbociclib to letrozole did not appear to affect pain outcomes, in either direction, as measured by the mBPI-sf.

Table 8: Efficacy Outcomes in the PALOMA-1 trial.[1]		
Treatment Groups	**Palbociclib + Letrozole**	**Letrozole alone**
Median follow-up, months	29.6	27.9
No. patients remaining on treatment, n (%)	19 (23)	8 (10)
Primary Outcome - Investigator Assessed PFS[A]		
Combined Cohorts (ITT population)	n=84	n=81
No. PFS events (%)	41(48.8)	59 (72.8)
Median PFS, months (95% CI)	20.2 (13.8-27.5)	10.2 (5.7-12.6)
Hazard ratio (95% CI; one-sided p-value)	0.49 (0.32-0.75; p=0.0004)	
Cohort 1	n=34	n=32
No. PFS events (%)	15 (44.1)[E]	25 (78.1)[E]
Median, months (95% CI)	26.1 (11.2-NR)	5.7 (2.6-10.5)
Hazard ratio (95% CI; one-sided p-value)	0.30 (0.16-0.57; p<0.0001)	
Cohort 2	n=50	n=49
No. PFS events (%)	26 (52)[E]	34 (69.4)[E]
Median, months (95% CI)	18.1 (13.1-27.5)	11.1 (7.1-16.4)
Hazard ratio (95% CI; one-sided p-value)	0.51 (0.30-0.85; p=0.0046)	
Secondary Outcome - BICR-assessed PFS[A,E]		
Combined Cohorts (ITT population)	n=84	n=81
No. PFS events (%)	31(36.9)	33 (40.7)
Median PFS, months (95% CI)	25.7 (17.7-NR)	14.8 (9.3-20.4)
Hazard ratio (95% CI; one-sided p-value)	0.62 (0.38-1.02; p=0.02)	
Cohort 1	n=34	n=32
No. PFS events (%)	11 (32.4%)	9 (28.1%)
Median, months (95% CI)	31.6 (11.2-NR)	38.6 (7.5-38.6)
Hazard ratio (95% CI; one-sided p-value)	0.73 (0.30-1.78; p=0.24)	
Cohort 2	n=50	n=49
No. of PFS events (%)	20 (40)	24 (49)
Median, months (95% CI)	20.3 (12.2-NR)	14.6 (8.1-20.0)
Hazard ratio (95% CI; one-sided p-value)	0.58 (0.32-1.05; p=0.03)	
Other Key Secondary Outcomes		
Combined Cohorts (ITT population)	n=84	n=81
Objective Response Rate[B] % (95% CI)	43(32-54)	33 (23-45)
One-sided p-value	p=0.13	
Complete response	1 (1)	1 (1)
Partial response	35 (42)	26 (32)
Stable disease	37 (44)	30 (37)
≥ 24 months	32 (38)	20 (25)
< 24 months	5 (6)	10 (12)
Progressive disease	3 (4)	18 (22)
Indeterminate	8 (10)	6 (7)

Table 8: Efficacy Outcomes in the PALOMA-1 trial.[1]		
Duration of Response[C]		
Median duration in months (95% CI)	20.3 (13.4-25.8)	11.1 (9.3-31.6)
	p=NR	
Clinical Benefit[D]		
No. (%) patients achieving clinical benefit (%)	68 (81)	47 (58)
One-sided p-value	p=0.0009	
Overall Survival		
No. deaths	30	31
Median, months (95% CI)	37.5 (28.4-NE)	33.3 (26.4-NE)
Hazard ratio (95% CI; two-sided p-value)	0.81 (0.49-1.35; p=0.42)	
Abbreviations: BICR - blinded independent central review; CI - confidence interval; ITT - intent-to-treat; No./n = number; 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.[2]		

Table 9: 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).[10]		
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

Adverse events (AEs) data,[1] which were reported for all patients receiving at least one dose of study medication (n=160), are summarized in Table 10. 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 (SAE) were reported as the number of patients reporting at least one SAE. Serious adverse events were reported at 8% in the palbociclib-letrozole group and these included pulmonary embolism, back pain and diarrhea. The number of SAE occurring in the letrozole group was unclear from the trial publication; however, the trial record indicates the incidence of SAE in the letrozole arm was 6%.[10] 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.

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

Table 10: Adverse events[A] in the PALOMA-1 trial.[1]				
Adverse Events, n (%)	**Palbociclib + Letrozole n=83**		**Letrozole alone n=77**	
Any grade adverse event	82 (99)		65 (84)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Any adverse event	19 (23)	63 (76)	49 (64)	16 (21)
Neutropenia	17 (20)	45 (54)	3 (4)	1 (1)
Leucopenia	20 (24)	16 (19)	2 (3)	0
Fatigue	30 (36)	4 (5)	17 (22)	1 (1)
Anemia*	24 (29)	5 (6)	4 (5)	1 (1)
Nausea	19 (23)	2 (2)	9 (12)	1 (1)
Arthalgia	18 (22)	1 (1)	10 (13)	2 (3)
Alopecia**	18 (22)	NA	2 (3)	NA
Diarrhea	14 (17)	3 (4)	8 (10)	0
Hot flush	17 (21)	0[B]	9 (12)	NA[B]
Thrombocytopenia	12 (14)	2 (2)	1 (1)	0
Decreased appetite	12 (14)	1 (1)	5 (6)	0
Dyspnea	11 (13)	2 (2)	5 (6)	1 (1)
Nasopharyngitis	13 (16)	0	8 (10)	0
Back pain	11 (13)	1 (1)	11 (14)	1 (1)
Headache	12 (14)	0	8 (10)	0
Vomiting	12 (14)	0	2 (3)	1 (1)
Asthenia	9 (11)	2 (2)	3 (4)	0
Bone pain	8 (10)	2 (2)	3 (4)	0
Constipation	10 (12)	0	7 (9)	0
Cough	10 (12)	0	8 (10)	0
Stomatitis	10 (12)	0	2 (3)	0
Epistaxis	9 (11)	0	1 (1)	0
Influenza	8 (10)	1 (1)	1 (1)	0
Muscoloskeletal pain	8 (10)	1 (1)	5 (6)	0
Upper respiratory tract infection	8 (10)	1 (1)	2 (3)	0
Dizziness	8 (10)	0	3 (4)	0
Peripheral neuropothy	8 (10)	0	4 (5)	0
Oropharyngeal pain	8 (10)	0	1 (1)	0
Pain in extremity	8 (10)	0	6 (8)	0
Any serious adverse event	7 (8)[C]		5 (6)[D]	
Adverse events leading to treatment discontinuation	11 (13)[E]		2 (3)[F]	

Abbreviations: n= number.

Notes:

[A] Most common all-cause adverse events that occurred in at least 10% of patients in the safety population.

[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 [2,10] 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).[2]

[D] Source: ClinicalTrials.gov trial record.[10]

[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).

6.4 Ongoing Trials

Two ongoing RCTs were identified that met the eligibility criteria of this review. PALOMA-2 is the phase 3 confirmatory trial for PALOMA-1.[23] PALOMA-4 is similar in design to PALOMA-2, but will assess palbociclib-letrozole compared to placebo-letrozole in an age restricted (18 to 70 years) Asian patient population.[24]

Table 11: Ongoing trials of palbociclib in combination with endocrine therapy vs. endocrine therapy alone in post-menopausal women with ER+/HER2- metastatic breast cancer.			
Trial Design	**Key Inclusion Criteria**	**Interventions and Comparators**	**Outcomes**
Trial NCT01740427 (PALOMA-2) Multicentre (320 sites), double-blind randomized phase 3 trial Start date: February 2013 Expected primary completion date: February 2016 Expected completion date: February 2017 Status: Ongoing (not recruiting patients) Estimated enrolment: 650 Sponsor: Pfizer	• ≥ 18 years old • Post-menopausal women • 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 0-2 • Adequate organ function • No prior neoadjuvant treatment with letrozole or anastrozole with disease-free interval ≥12 months from completion of 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.	<u>Palbociclib + Letrozole</u> 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. <u>Placebo + Letrozole:</u> 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 • Disease control (defined as CR, PR or SD ≥24 weeks according to RECIST) • QOL (EQ-5D, FACT-B)

Table 11: Ongoing trials of palbociclib in combination with endocrine therapy vs. endocrine therapy alone in post-menopausal women with ER+/HER2- metastatic breast cancer.			
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.	<u>Palbociclib + Letrozole</u> 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. <u>Placebo + Letrozole:</u> 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: 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 comparing palbociclib with other therapies as first-line treatment in post-menopausal women with ER+ and HER2- ABC.[11]

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. Other comparators were considered in a sensitivity analysis and included treatments approved for use in Canada but not publically funded (i.e., fulvestrant 250mg or 500mg intramuscular injection monthly) or used in later lines of treatment (i.e., everolimus 10mg daily-exemestane 25mg daily). The outcomes of interest were progression-free survival or time-to-progression (PFS/TTP) and overall survival (OS).

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 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 and 95% credible intervals were used to measure the association between treatments for efficacy. Other effect measures reported included the following:

- Mean rank with 95% credible intervals (values range from 0-1, 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 approaches (e.g. graphical and tabular summaries) 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 advanced/metastatic disease
- Consideration of the PALOMA-1 cohort only, and PALOMA cohorts treated as separate studies
- Percentage of patients hormone-receptor positive (HR+)
- Variation in defining PFS-TTP endpoints
- Inclusion of crossover studies
- Blinding in studies

Results

Nine trials met the eligibility criteria of the NMA, however two trials did not report outcome data, which left seven trials (consisting of 2859 patients) for inclusion. A brief summary of the characteristics of these trials was provided in the submitted NMA, and has been reproduced in Table 12. The results of the individual trials are summarized in Table 13. For each outcome the evidence network was comprised of 5 direct comparisons, with single trials informing three of these comparisons, and 10 pairwise comparisons in total. Figure 1 depicts the evidence network for PFS/TTP. The evidence network for OS is identical to the one shown in Figure 1 and therefore has not been included in this report.

The NMA found a statistically significant difference in PFS/TTP in favour of palbociclib-letrozole relative to letrozole, anastrozole, and exemestane (Table 14). 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, or exemestane.

Table 12: Summary of individual trials included in the manufacturer submitted network met-analysis.					
Trial Publication	**n**	**Design**	**Patient Population* (Line of treatment, % ER/PgR+, and % with metastases)**	**Prior adjuvant endocrine therapy (% Patients)**	**Intervention and Comparator**
Bonneterre 2000	668	DB	1st-line, 45% ER/PgR+, Metastases: 34% visceral 31% bone 15% bone only	7.6%	Anastrozole vs. tamoxifen
Finn 2015 (PALOMA-1)	165	OL	1st-line, 100% ER/PgR+ Metastases: 48% visceral 18% bone 18% bone only	33%	Palbociclib-letrozole vs. letrozole
Iwata 2013	292	DB	1st-line, 74.3% ER/PgR+ Metastases: 50% visceral 27% bone 27% bone only	NR	Exemestane vs. anastrozole
Llombart-Cussac 2012	103	OL	1st/2nd-line, 100% ER/PgR+ Metastases: 52% visceral NR bone NR bone only	50%	Exemestane vs. anastrozole
Mouridsen 2001	907	DB	1st/2nd-line, 100% ER/PgR+ Metastases: 44% visceral 30% bone 16% bone only	18%	Letrozole vs. tamoxifen
Nabholtz 2000	353	DB	1st-line, 89% ER/PgR+ Metastases: 48% visceral 60% bone 25% bone only	12%	Anastrozole vs. tamoxifen
Paridaens 2008	371	OL	1st/2nd-line, 93% ER/PgR+ Metastases: 47% visceral 35% bone 12% bone only	20.8%	Exemestane vs. tamoxifen
Abbreviations: DB - double blind; ER - estrogen receptor; OL - open-label; NR - not reported; PgR - progesterone receptor.					
Notes: * All patients were post-menopausal and had no prior endocrine therapy for metastatic disease.					

Table 13: 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 arms	PFS/TTP		OS	
		HR	95% CI*	HR	95% CI*
Bonneterre 2000	Anastrozole vs. tamoxifen	1.01	0.79-1.29**	1.06	0.92-1.27***
Finn 2015 (PALOMA-1)	Palbociclib-letrozole vs. letrozole	0.49	0.32-0.75	0.81	0.49-1.35
Iwata 2013	Exemestane vs. anastrozole	0.99	0.76-1.3	0.94	0.65-1.36
Llombart-Cussac 2012	Exemestane vs. anastrozole	1.13	0.75-1.72	1.33	0.78-2.25
Mouridsen 2001	Letrozole vs. tamoxifen	0.7	0.6-0.82	1.01	0.9-1.14****
Nabholtz 2000	Anastrozole vs. tamoxifen	0.69	0.54-0.9**	0.98	0.81-1.23***
Paridaens 2008	Exemestane vs. tamoxifen	0.84	0.67-1.05	1.13	0.85-1.5

Abbreviations: CI - confidence interval; HR = hazard ratio; OS - overall survival; PFS - progression-free survival; TTP -time-to-progression.

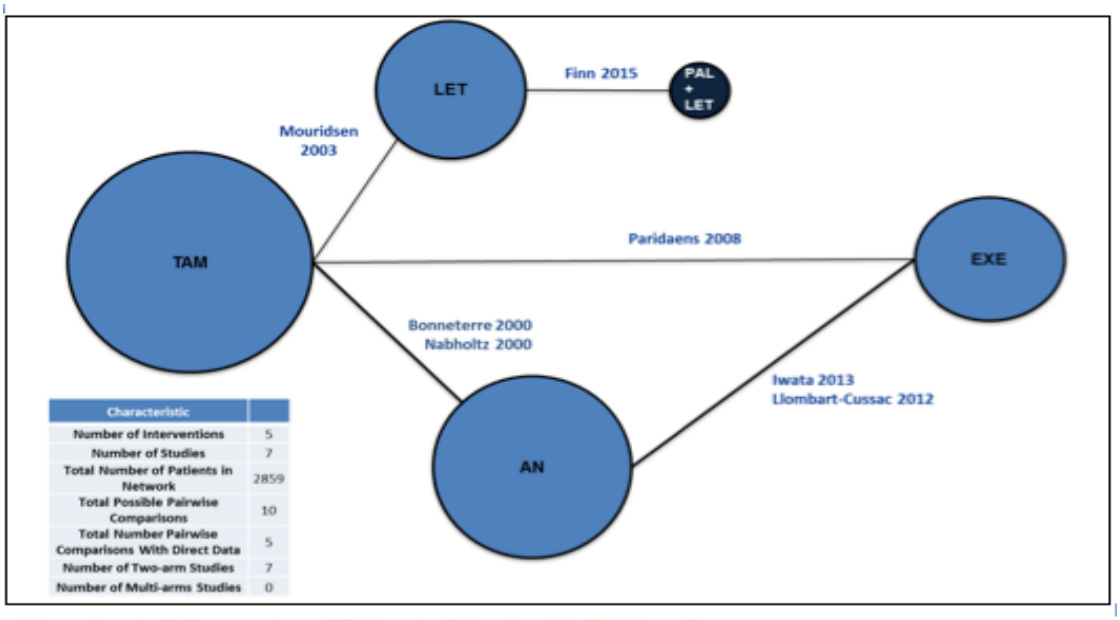
Notes:
* p-values were not reported.
** Confidence intervals were estimated from reported HRs and p-values using methods by Altman (2011).
*** Upper limit of confidence interval was manually calculated using statistical formula.
**** Hazard ratios were calculated using the methods of Tierney (2007).

Table 14: Summary of NMA results for progression-free survival (or time-to-progression) and overall survival.

Treatment Comparison	PFS/TPP*		OS*	
	HR	95% Credible Interval	HR	95% Credible Interval
Palbociclib-letrozole vs. letrozole	0.49	0.32-0.75	0.82	0.49-1.34
Palbociclib-letrozole vs. anastrozole	0.41	0.25-0.66	0.80	0.47-1.35
Palbociclib-letrozole vs. exemestane	0.40	0.25-0.65	0.74	0.43-1.29
Palbociclib-letrozole vs. tamoxifen	0.34	0.22-0.54	0.82	0.49-1.38

Abbreviations: HR = hazard ratio; OS - overall survival; PFS - progression-free survival; TTP -time-to-progression.

Notes:
* Results based on fixed-effects modeling.



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

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

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.[25] The full quality assessment, which can be found in Appendix B, identified a number of limitations associated with 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 NMA primarily 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. Everolimus-exemestane is currently approved and reimbursed in Canada for second-line therapy. Data on this combination as first-line therapy are from a subgroup analysis (from a randomized trial). In the absence of these data, however, it does not necessarily mean a comparison between combination and single-agent therapies is a more appropriate or acceptable comparison. It is quite likely that a combination treatment of two effective components (i.e., palbociclib-letrozole) with distinctive pharmacological mechanism of actions is better than monotherapy in terms of efficacy. Furthermore, the submitted NMA did not explore the comparative safety or quality of life between palbociclib-letrozole and the single-agents investigated, which presumably would be important when a combination therapy is compared to a single therapy. Of interest to note is that another trial evaluating a combination therapy (anastrozole-fulvestrant) was also omitted from the NMA for reasons that are unknown.[26]

- The patient populations of included trials are not entirely relevant since not all patients were HR+ (range, 45%-93% in four of the seven trials), the HER2 status of patients was not reported, and a proportion of patients, albeit small, were treated in the second-line setting with chemotherapy. Some of these issues may 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, is considered insufficient for the following reasons:

- The PALOMA-1 trial had multiple flaws in design and execution, raising concern over the true PFS benefit associated with palbociclib-letrozole. These issues remain in the NMA despite a sensitivity analysis performed using retrospective BICR assessment data.
- There is notable heterogeneity across trials (e.g., proportion of patients HR+, inclusion of 2nd-line patients, blinding) even though the authors did a range of sensitivity analyses based on study and patient characteristics. The authors acknowledged that the data were limited in terms of the small number of trials and small sample size. These limitations could have compromised the usefulness of sensitivity analysis in identifying any possible differences between various subgroups.
- The influence of important patient characteristics was not fully explored making it difficult to determine whether the effect estimates obtained were solely due to differences in treatments. The HER2 status of patients in included trials was not addressed in the NMA so it is unknown whether all included patients were HER2-. As noted above, not all trials included HR+ patients. The influence of hormone status was analyzed in a sensitivity analysis; however, this analysis was not restricted to trials in which 100% of patients were HR+ but instead included trials in which >75% were HR+.
- Eligible trials were required to report both PFS and OS data. This strategy is problematic because it may omit trials reporting PFS only, for example, which would have led to an incomplete or selective evidence base.
- 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 included in 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. At least two trials are known to be missing from the analysis,[12,26] which demonstrates selective reporting and publication bias are also concerns in this NMA.

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 NMA found a statistically significant difference in PFS/TTP in favour of palbociclib-letrozole relative to letrozole, anastrozole, and exemestane. Palbociclib-letrozole was also associated with the highest probability of being the best treatment option. All sensitivity analyses performed indicated the PFS results were robust to differences in the patient or study characteristics assessed. No differences in overall survival were demonstrated. 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 analysis (versus only single-agent regimens) as well as other outcomes (adverse events, quality of life) and significant heterogeneity across included trials. The conclusions drawn from the NMA should be interpreted with caution.

8 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 Initial Clinical Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Clinical Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Clinical Guidance Report will supersede this Initial Clinical Guidance Report.

The pCODR 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: Appraisal of the manufacturer-submitted network meta-analysis (NMA), comparing palbociclib-letrozole to other therapies,[11] using the ISPOR Questionnaire to assess Relevance and Credibility.[25]

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.
- 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. Subgroup data are available from a randomized trial evaluating everolimus-exemestane. These data were excluded from the primary analysis of both outcomes (because subgroup data were ineligible) but were included in a secondary analysis. Another trial known to pCODR comparing anastrozole-fulvestrant to anastrozole alone was omitted from the NMA for unknown reasons.[26]

[C] Comparative data on adverse events and/or quality of life were not provided although it was indicated that such analyses were performed separately from the submitted NMA. 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]			
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	Yes		X[C]	
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] The complete systematic review was not provided to pCODR. While the methods used to search for evidence appeared comprehensive (i.e., information sources, search strategies), the submitted NMA did not include a list of all trials excluded from the review. pCODR identified a trial that should have been included in the NMA.[26]

[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 outcomes reported in each trial were not provided. It is concerning that trials were eligible for inclusion into the NMA if they reported changes in *both* progression-free survival (or time-to-progression) and overall survival. This implies that a trial was excluded if it did not report both outcomes and could lead to an incomplete or selective evidence base. In addition, 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 (i.e., chemotherapy).
- In four trials not all patients were hormone-receptor positive (range, 45-93%) as a result of some trials including patients with unknown hormone status. A sensitivity analysis was performed excluding trials with <75% of patients who were hormone-receptor positive, however, the rationale for using this arbitrary cut-off point was not provided.
- The HER2 status of included patients was not indicated.
- Three trials were open-label. Although a sensitivity analysis was performed using the effect estimate obtained from a blinded central review of the PALOMA-1 trial, the assessment was retrospective and blinded central review was not available for the two other open-label trials.
- The definitions of progression-free survival/time-to-progression 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 inconsistency between direct and indirect evidence; 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, data are missing for another important patient characteristic (i.e., HER2 status) while another characteristic was only arbitrarily explored (e.g. hormone status).						
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.						
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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