CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Fulvestrant (Faslodex) for Metastatic Breast Cancer

February 1, 2018

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TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding fulvestrant (Faslodex) for metastatic breast cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

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

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

1.1 Introduction

The objective of this review is to evaluate the effectiveness and safety of fulvestrant (Faslodex) for the treatment of postmenopausal women with non-visceral locally advanced or metastatic HER2- breast cancer, regardless of age and who have not been previously treated with endocrine therapy. This is different from the Health Canada regulatory approval which is for the treatment of postmenopausal women with estrogen receptor-positive, human epidermal growth receptor 2 (HER2)-negative locally advanced or metastatic breast cancer not previously treated with endocrine therapy.

Fulvestrant is a selective estrogen receptor antagonist. The recommended dose is 500 mg administered intramuscularly as two 5 mL (250 mg/5 mL) injections, one in each buttock administered on days 0, 14, 28 and then every 28 days thereafter.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Two randomized controlled trials were identified as part of the systematic review.[1,2] Visceral disease (yes and no) were subgroups considered in both the FALCON and FIRST studies. The FALCON study is a phase III, double-blind, superiority, international, multi-centered RCT which compared the efficacy and safety of fulvestrant to anastrozole among post-menopausal patients who had not received previous endocrine therapy.[1] The FIRST study was a phase II, open-label, non-inferiority, international, multi-centered RCT that preceded FALCON and also compared fulvestrant with anastrozole as first-line endocrine therapy for advanced hormone receptor-positive breast cancer in post-menopausal women.[2] FALCON randomized 462 patients and FIRST randomized 205 patients in a 1:1 ratio to either fulvestrant or anastrozole. Both studies included patients with hormone receptor positive status, locally advanced or metastatic breast cancer who were not amenable to therapy of curative intent, and WHO performance status 0-2. The primary endpoint in FALCON was progression-free survival (PFS) and in FIRST was clinical benefit

rate (CBR). Clinical benefit rate was defined as the proportion of all randomly assigned patients who had a best overall response of a complete response, a partial response, or stable disease for at least 24 weeks.

Highlights of key outcomes in the FALCON and FIRST trials are presented in Table 1 for the pre-specified subgroup analysis in patients with non-visceral disease involvement. Results on efficacy and corresponding p-values in subgroup analysis cannot be interpreted with rigour and validity therefore all conclusions should be made with caution.

Table 1: Highlights of Key Outcomes in FALCON and FIRST among patients with non-visceral disease[3]

	FALCON		FIRST	
	Fulvestrant (N=95)	**Anastrozole (N=113)**	**Fulvestrant (N=54)**	**Anastrozole (N=45)**
Median follow-up, months	25.72	25.23	60.8	39.3
Patients remaining on treatment, n (%)	34 (35.8)	26 (23.0)	41 (85.4)	27 (46.6)
Primary Outcome (FALCON) – PFS				
No. PFS events (%)	51 (53.7)	79 (69.9)	26 (48.1)	30 (66.7)
Median PFS, months (95%CI)	22.3 (16.6-32.8)	13.8 (11.0-16.6)	34.0 (24.1-44.4)	21.3 (13.1-31.6)
HR (95%CI, two-sided p value)	0.592 (0.419-0.837; p = 0.0030)		0.58 (0.34-0.99; p = 0.05)	
Primary Outcome (FIRST) – CBR				
No. (%) patients achieving clinical benefit	83 (87.4)	85 (75.2)	46 (85.2)	30 (66.7)
OR, 95%CI, p-value	2.242 (1.087-4.866; p = 0.0285)		2.875 (1.110-7.933; p = 0.029)	
OS				
No. OS events (%)	18 (18.9)	33 (29.2)	29 (53.7)	26 (57.8)
Median OS, months (95%CI)	NC	NC	76.6	60.9
HR (95%CI, two-sided p value)	0.601 (0.347-1.042; p = 0.0696)		0.68 (0.40-1.18; p = 0.171)	
HrQoL[4]				
Among the total population in the FALCON trial, there was no clinically meaningful difference in the proportion of patients who had improved FACT-B total score and TOI with fulvestrant compared with anastrozole. HrQoL was not assessed in the FIRST trial.				
Harms Outcome, n (%)[3]	**N=95**	**N=113**	**N=54**	**N=45**
AE (any grade)	76 (80.0)	80 (70.8)	37 (68.5)	28 (62.2)
Grade ≥3	22 (23.3)	25 (22.1)	10 (18.5)	5 (11.1)
SAE	11 (11.6)	19 (16.8)	7 (13.0)	4 (8.9)
Discontinuation due to AE	8 (8.4)	5 (4.4)	2 (3.7)	0

Abbreviations: AE = adverse event, **CBR** = clinical benefit rate, **CI** = confidence interval, **FACT-B** = Functional Assessment of Cancer Therapy for Breast Cancer, **HR** = hazard ratio, **HRQoL** = health-related quality of life, **NA** = not applicable, **NR** = not reported, **OR** = odds ratio, **OS** = overall survival, **PFS** = progression-free survival, **SAE** = serious adverse event, **TOI** = Trial Outcome Index
Notes: *HR < 1 favours fulvestrant

With respect to the magnitude and direction, the efficacy results of the non-visceral subgroups are similar to that of the overall trial results; the overall trial results in FALCON suggest that fulvestrant significantly extends PFS compared with anastrozole and results in the FIRST study suggest that fulvestrant is not inferior to anastrozole with respect to CBR. With respect to harms outcomes, overall rates of adverse events (any grade, grade ≥3, serious, and discontinuations) were similar in the non-visceral subgroups compared to the overall trial results of FALCON and FIRST.

Limitations

The main limitation with respect to both the FALCON and FIRST trials is that patients with non-visceral disease represented subgroups of the total trial populations. Visceral disease involvement was a subgroup in both trials; subgroup analyses are likely to lack power to detect differences, so most significant results may represent false positive results. Of note, in either trials, visceral involvement was not reported as a pre-planned subgroup. Visceral involvement was not a stratification factor at baseline in either studies and balance of baseline patient characteristics may not hold; these imbalances of prognostic factors and effect modifiers may have biased results in favour of fulvestrant in FALCON. Overall, results from the non-visceral disease patient subgroups should be interpreted with caution due to the small number of patients in the subgroups; at most results are hypothesis generating.

The Submitter provided feedback on the pCODR Initial Recommendation which stated "The non-visceral subgroup from the FALCON study was pre-specified. For FALCON the visceral group was specified after the finalization of the protocol, and included in the Statistical Analysis Plan (SAP) which was finalized prior to database lock and unblinding." Please see 6.3.3 Limitations/Sources of Biases for further details on dates. In summary, the protocol amendment was reported to have been made at the time recruitment started;[5] however, there remains uncertainty on the timing of when visceral involvement was included in the Clinical Study Protocol (CSP) in relation to the data cut-off date as well as finalization of the SAP. Although the non-visceral subgroup was reported to be pre-specified according to the Submitter, it was not pre-specified at the trial onset and thus not included in the original CSP/SAP.

In most cases, subgroup analyses are exploratory in nature and only indicative of possible subgroup effects; they do not have the statistical strength to support credible conclusions on treatment effects.[6] Subgroup analyses are enhanced by: biological plausibility of the proposed differential effect, support for consistent and similar findings from a number of studies, a priori predicted subgroup effects, and use of statistically sound methods to compensate for or adjust the type I error rate.[6-10] According to the Clinical Guidance Panel, there is some support for consistent and similar findings for the use of fulvestrant in this setting within the non-visceral subgroup (i.e., from FIRST), however, the predicted subgroup effect was not reported a priori and statistical methods were not reported to adjust for the type I error rate. The biological plausibility of the proposed differential effect is also uncertain as a rationale was not identified. It was reported that a range of post-hoc analyses have been performed, including exploration of baseline characteristics that could have influenced efficacy, failed to identify a clear biological explanation for the finding in the visceral disease subgroup.[4] As more credible conditions are met (i.e., biological plausibility of the proposed differential effect, support for consistent and similar findings from a number of studies, a priori predicted subgroup effects, and use of statistically sound methods to compensate for or adjust the type I error rate), this increase the confidence that there are real treatment differences with fulvestrant by visceral involvement; based on the FALCON trial, only some credible conditions have been met.

Further key limitations specific to individual trials are listed below.

FALCON

- A global interaction test was completed with a Cox-proportional hazard model to assess whether the treatment effect was consistent across the covariates.[1] A post-hoc interaction test to assess for consistency of the treatment effects across the visceral and non-visceral subgroups was also done.[1] Treatment effects were

reported to be largely consistent across the pre-specified patient subgroup (global interaction test p=0.1061) in demonstrating no significant differential treatment effect by each covariate. The post-hoc interaction test across visceral and non-visceral subgroups gave a significant p-value of 0.0092.[1] According to the Clinical Study Report for FALCON, if the global interaction test was significant then the covariate by treatment interaction would be assessed individually.[3] The global interaction test was not significant, however, a post-hoc interaction test was conducted for the covariate of visceral involvement. The Clinical Study Report noted "treatment effect may be investigated in groups as defined by these covariates to locate the source and nature of any interactions or if that would aid interpretation of the trial results."[4] As the global interaction was "only marginally greater than the 10% significance level, it is pertinent to closely examine the consistency of the observed treatment effect across all pre-defined subgroups".[4] A global interaction test was conducted and suggested there were no statistically significant effect modifiers of fulvestrant identified, this includes the non-visceral disease subgroup. Given the small sample size in this subgroup analysis, it is possible that the test for interaction wasn't powered to determine statistical difference. The rationale for the subgroup analysis of visceral disease involvement was not reported and authors reported it is unknown why there is an observed difference in benefit by visceral disease involvement.

- The very large number of major protocol deviations that occurred during the trial was concerning (45.2% in the fulvestrant group and 33.6% in the anastrozole group). Most frequent deviations included mis-stratification and RECIST timing issues. While sensitivity 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. Of note, EMA assessment reported that these deviations are considered unlikely to affect the robustness of the study.[11]
- Patients with prior endocrine therapy for breast cancer were excluded, thus generalizability to the Canadian setting, where patients are commonly treated with endocrine therapy in the neoadjuvant or adjuvant setting, is unknown.

FIRST

- The trial was an exploratory study. The trial was open-label and therefore, investigators and patients were not blinded to treatment assignment. Therefore, the trial is at a high-risk for a number of different biases that can affect the internal validity (e.g., patient selection for eligibility, performance bias due to knowledge of assigned treatment).
- There were multiple data-driven amendment changes (three amendments for follow-up analyses) that compromised the statistical analysis plan of the trial and cast doubt on the integrity of the obtained results and the magnitude of the reported treatment effect estimates.

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

From a patient's perspective, managing a diagnosis of metastatic breast cancer is challenging, as current treatment options for metastatic breast cancer are only effective at prolonging progression-free disease, and most cases of advanced disease will progress and symptoms will worsen. Rethink and CBCN indicated that the many effects of

metastatic breast cancer represent a significant or debilitating impact (both physical and social) on patients' and caregivers' quality of life. Rethink and CBCN reported that bone pain, insomnia, fatigue, muscle weakness, shortness of breath, nausea, and loss of appetite were the most common symptoms experienced as a result of breast cancer. Patients indicated that ability to work, ability to perform household chores, ability to travel and pursue personal hobbies and interests were impacted by breast cancer.

Provincial Advisory Group (PAG) Input

Clinical factors:

- Clarity on the eligible patient group
- Advice on sequencing of current treatments and place in therapy

Economic factors:

- Requires nursing to administer intramuscular injections monthly

Registered Clinician Input

Overall, clinicians providing input note that hormone receptor positive advanced breast cancer is prevalent in post-menopausal women. Based on trial evidence, clinicians state that fulvestrant is more effective and has lower toxicity than anastrozole in patients with locally advanced or metastatic breast cancer. However, the survival benefit is reported to be non-significant in patients with visceral disease and those with a history of prior chemotherapy. Therefore, first-line therapy with fulvestrant would be appropriate in low- or intermediate-risk advanced or metastatic disease with good prognosis (e.g., non-visceral disease), high-risk patients with comorbidities who are not eligible for combination targeted therapies. The drug would be used as an alternative to aromatase inhibitors (letrozole) + CDK4/6 inhibitors (palbociclib and ribociclib), and in patients for whom CDK4/6 inhibitor is not indicated, e.g., those who are unable to tolerate CDK4/6 inhibitor, or those who have comorbidities. One clinician expressed concerns over considering fulvestrant as a first line treatment option for hormone-receptor positive metastatic breast cancer, due to uncertainties around clinical and safety advantages of fulvestrant over existing alternative treatments.

Summary of Supplemental Questions

Critical appraisal of the manufacturer-submitted network meta-analysis (NMA) comparing fulvestrant to palbociclib plus letrozole in the non-visceral population.

The Manufacturer submitted a NMA comparing fulvestrant to palbociclib plus letrozole. Details of the underlying systematic review methodology were provided for the full NMA. However, for the non-visceral disease subgroup NMA, no further methodology is reported except that trials were selected if they included fulvestrant or palbociclib plus letrozole. Based on the limited reporting on the methodology for the subgroup NMA, critical appraisal of the submitted NMA was limited by the lack of information. The results of the NMA indicated that treatment with fulvestrant compared to palbociclib plus letrozole were not statistically significant for PFS and OS. Treatment with fulvestrant compared to anastrozole statistically improved PFS and OS. Studies appeared similar enough to be compared. In order to conduct the indirect comparison, it was assumed equivalence of anastrozole to letrozole, this was considered reasonable. However, the assumption of proportional hazards was not tested for PALOMA-1. The results of the NMA should be viewed in light of these underlying assumptions (AIs have similar efficacy, definition of non-visceral, and assumption of proportional hazards) used to conduct this analysis. Overall, given these assumptions and the limited reporting on the methodology for the subgroup NMA, the comparative efficacy of fulvestrant to palbociclib plus letrozole is

uncertain. This appears to align with the reported results of the NMA which indicate that treatment with fulvestrant compared to palbociclib plus letrozole were not statistically significant for PFS and OS, i.e., the results failed to demonstrate a difference in treatment effect in favour of one treatment over the other.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

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

Table 2: Assessment of generalizability of evidence for fulvestrant for locally advanced or metastatic breast cancer

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	**WHO PS**	Most patients in the trials had WHO PS 0-1 FALCON (n=462): WHO PS 0: 232 (50%); WHO PS 1: 211 (46%); WHO PS 2: 19 (4%) FIRST (n=205):[3] WHO PS 0: 110 (54); WHO PS 1: 83 (40%); WHO PS 2: 12 (6%)	Do the trial results apply to patients with a WHO PS of 2 or greater? If so, why?	The CGP note that either one of the studies enrolled patients with performance status of 3 while small numbers of patients of performance status 2 were enrolled. However, based on clinical practice the CGP noted that patients with PS 3 would be treated with an aromatase inhibitor therefore it would be reasonable to use fulvestrant in patient's up to PS 3 based on the discretion of the treating oncologist.
	Disease Stage	Most patients in the trials had metastatic (versus locally advanced) disease FALCON (n=462): Locally advanced: n=60 (13%); Metastatic: n=402 (87%) FIRST (n=205): Locally advanced: 37 (18%); Metastatic: n=168 (82%)	Is this representative of how patients present in Canadian practice? Does this limit the interpretation of the trial results to patients with metastatic disease?	The CGP agree that the distribution of locally advanced to metastatic disease in the two included trials is mostly representative of the clinical population. The FIRST trial did have a less representative number of locally advanced patients
	Prior endocrine therapy in adjuvant setting	PAG is also seeking clarity on whether patients treated with endocrine therapy in the adjuvant setting would be eligible for treatment with fulvestrant for locally advanced or metastatic disease. FALCON: Excluded patients with prior hormonal treatment for breast cancer FIRST: Included patients who received adjuvant endocrine therapy for early disease, provided it was completed more than 12 months before random assignment	Do the trial results apply to patients who were treated with endocrine therapy in the adjuvant setting?	The CGP agreed that only patients who are naïve to endocrine therapy should qualify for treatment with fulvestrant. This would not include those patients who have received endocrine therapy in the adjuvant setting. Other randomized trials combining fulvestrant with other hormonal therapies have demonstrated benefit only when sufficiently large numbers of de-novo metastatic and locally advanced breast cancer patients were included. Therefore it is unlikely that these results are generalizable to hormonal therapy exposed patients, including 2nd line or later line patients
Comparator	**Standard of Care**	PAG noted current endocrine therapies for locally advanced or metastatic endocrine receptor positive breast cancer in postmenopausal women include aromatase inhibitors or tamoxifen. PAG noted that anastrozole in the comparator arm in the FALCON trial is an appropriate comparator.	Are the findings of the trials limited to anastrozole, or are they generalizable to other endocrine therapies? Why or why not?	The CGP agree that the results of the trial are generalizable to the Canadian population who would be receiving aromatase inhibitors or tamoxifen in clinical practice.
Abbreviations: PAG = Provincial Advisory Group, **WHO** = World Health Organization Performance Status				

1.2.4 Interpretation

Metastatic breast cancer is the second most common cause of cancer-related death among Canadian women. Although incurable, 22% of those suffering with metastatic breast cancer can expect to remain alive 5 years after diagnosis. Although literature does not strongly support the surrogacy of PFS for OS in breast cancer, the prolonged expected survival of ER+/HER2- disease has resulted in the use of progression-free survival (PFS) as a clinically meaningful endpoint when considering treatment selection in the 1st line setting. PFS may be especially meaningful when considering hormonal therapy, given its relative lack of toxicity, ease of administration, and limited requirements for monitoring.

The FIRST and FALCON studies were both designed to compare 1st line fulvestrant to anastrozole in ER+/HER2- advanced breast cancer in patients. The FALCON study, a phase III, double-blind, placebo controlled trial met its primary end-point of improved PFS for fulvestrant vs. anastrozole. However, on pre-planned subgroup analysis, only the patients with non-visceral disease appeared to benefit statistically or clinically from fulvestrant, with an absolute median improvement in PFS of 8.5 months over anastrozole (HR 0.59, 95%CI 0.42–0.84, p = 0.0030), compared with 2.1 month determent in the visceral subgroup (HR 0.99, 95%CI 0.74–1.33, no p-value provided). Although this subgroup analysis lacks power to detect a difference, the CGP agreed that this is a clinically meaningful finding likely to be real. Although, the non-visceral disease group represented just under 40% of the total patients enrolled in the FALCON trial, the magnitude of effect was large enough to drive a statistically significant risk reduction for progression in the entire trial population of 0.797 (95%CI 0.637–0.999), but with a clinically less relevant difference in median PFS of 2.8 months. Given the similar results reported in the randomized phase II FIRST trial, the benefit of fulvestrant over other single-agent aromatase inhibitors is likely in this setting.

The FIRST and FALCON trials are consistent, decreasing the uncertainty of benefit of fulvestrant over anastrozole, with important clinical limitations. Firstly, patients eligible for both trials must have been hormone therapy naïve. Patients who had received adjuvant hormonal therapy for early breast cancer were excluded from both trials. This exclusion is consistent with randomized trials combining fulvestrant with other hormonal therapies being only of benefit when sufficiently large numbers of de-novo metastatic and locally advanced breast cancer patients were included. It is unlikely that these results are generalizable to hormonal therapy exposed patients, including 2nd line or later line patients. Patients with metastatic breast cancer only previously exposed to chemotherapy could still be eligible for 2nd line fulvestrant (1st line of hormonal therapy in a hormone therapy naïve patient), but this subset of patients is unlikely to exist in the real-world given standard global practice for non-visceral metastatic breast cancer patients. Secondly, in both trials, the majority of benefit was accrued by patients with non-visceral metastases, limiting generalizability to all metastatic breast cancer patients. The data are likely generalizable to patients with ECOG PS 3, since there is no biologic plausibility to suggest otherwise, save for higher hazard for death.

The toxicity profile of fulvestrant is comparable to anastrozole with similarly small numbers of patients discontinuing therapy. The overall health related quality of life, as measured by FACT-B and TOI were neither statistically different nor signal significant treatment-related detriment of quality of life for patients receiving fulvestrant. Any grade adverse events was numerically higher in the non-visceral subgroup of patients treated with fulvestrant vs. anastrozole by 10%, but this did not translate to a difference in the overall trial population. Arthralgia, hot flashes, fatigue, and nausea were experienced by >10% of patients treated with fulvestrant, in keeping with clinical expectations from the use of 2nd and 3rd generation hormonal therapy in this patient population.

Although new therapies have been developed and approved for use in metastatic ER+/HER2- advanced breast cancer, specifically CDK4/6 inhibitors, these treatments create a level of complexity and increased toxicity compared with AI therapy not seen with fulvestrant. Fulvestrant may be a more desirable treatment for patients for whom adherence to oral therapy may be a concern, who would prefer not to undergo regular phlebotomies, and who place a greater value on the maintenance of quality of life. This is in alignment with input from registered clinicians. This may be especially true for more marginalised oncologic populations including older patients, or patients averse to additional pills. Given data from PALOMA-3 demonstrating that CDK4/6 inhibition in combination with fulvestrant is more efficacious than fulvestrant alone, the combination in the first line setting in hormonal therapy naïve patients is potentially valuable. However, PALOMA-3 specifically studied this combination after failure of an AI and so such data are not generalizable to the relevant patient population and would require a separate review to assess for efficacy and safety. Combination therapies studied in phase III randomized controlled trials are required.

A systematic review and network meta-analysis was also conducted to assess the clinical efficacy, safety, and tolerability of hormonal therapies for patients with locally advanced or metastatic breast cancer. Twenty-two RCTs were included in the network meta-analysis allowing for comparisons between tamoxifen, anastrozole, letrozole, exemestane, fulvestrant, and palbociclib + letrozole. In the base-case and in sensitivity analysis, PFS for fulvestrant was statistically superior to anastrozole, tamoxifen, and exemestane as reported by the model, but only numerically superior to letrozole. The CGP noted that anastrozole and letrozole have been shown to be equivalent treatments and so fulvestrant should also be viewed as superior in this regard. When fulvestrant was compared to palbociclib + letrozole, PFS was significantly shorter than fulvestrant in the base-case (HR=1.609). In the sensitivity analysis, palbociclib + letrozole was no longer statistically superior to fulvestrant, but was numerically superior to fulvestrant. Given limitation identified with the indirect analysis, mainly the lack of data to conduct a critical appraisal, there is considerable uncertainty in the results that are reported for the comparison between fulvestrant and palbociclib plus letrozole. The GCP agree that there is currently no evidence to determine which therapy may be more superior.

1.3 Conclusions

The CGP concluded that there is a net clinical benefit to the use of fulvestrant in ER+/HER2- locally advanced or metastatic breast cancer with non-visceral disease, who have not been previously exposed to hormonal therapy in any setting, including in the adjuvant setting. This is based on the FALCON and FIRST trials. From a clinical perspective:

- A statistically significant and clinically meaningful improvement in the absolute median PFS benefit of 8.5 months was achieved in this subgroup of non-visceral patients in FALCON. The hazard ratio was consistent across both studies, despite an absolute median PFS improvement of 12.7 months in FIRST.
- Mature OS data are unavailable, but are unlikely to show a significant benefit given that the trial is not powered to detect a potential difference and the significant number of years needed to accumulate events. Although FIRST did suggest an overall survival advantage of fulvestrant over anastrozole, given the study's limitations, this result cannot be interpreted as conclusive.
- The CGP acknowledged the limitations in the FALCON trial as the subgroup of patients with non-visceral disease was not powered to detect a difference. Given the alignment of results with the FIRST trial and magnitude of absolute mPFS results, it is likely that a true treatment effect is present. Based on this, the CGP disagree with input from a registered

clinician which indicated that fulvestrant does not provide any meaningful improvement in important outcomes.

- Neither study enrolled patients with performance status of 3 and small numbers of patients of performance status 2 were enrolled. However, the CGP felt that this data is generalizable to all applicable patients with performance status <4.
- The CGP did note a high potential for indication creep. Fulvestrant could be used by clinicians in patients with visceral metastases or in later lines of therapy, including after CDK4/6 inhibitors or in combination with CDK4/6 inhibitors. The CGP felt that use of fulvestrant in patients with visceral metastases is not unreasonable given absence of a signal of determent, but this treatment would add additional cost without improving outcomes in this patient population. However, the CGP did feel that fulvestrant should be considered for use in patients for whom oral medication adherence or tolerability is suspect.
- Health-related quality of life was not adversely affected by the use of fulvestrant, as measured by FACT-B and TOI. Toxicity was not marked different between the fulvestrant and anastrozole.
- Additional nursing visits or clinic visits will be required for the administration of fulvestrant.
- No evidence exists for the use of CDk4/6 inhibitors in combination with fulvestrant in the population of interest and should not be expanded for use in this setting at this time until the available evidence for this combination is assessed to determine the comparative efficacy and safety.
- There is insufficient data to recommend CDK4/6 inhibition in combination with an aromatase inhibitor versus fulvestrant at this time. Patient values and preferences, and clinical factors should guide treatment selection.
- The CGP noted registered clinician input indicated a potential for expanding the use of fulvestrant as an option for second-line therapy after CDK4/6 agents. The CGP do not support such an expansion of the reimbursement population as there is no evidence to support this use.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Breast Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Breast cancer is the most common cancer in Canadian women. In 2016, an estimated 26,000 women were diagnosed with breast cancer and an estimated 6,000 women died of this disease.[12] Although most women diagnosed will be discovered at an early stage of disease, some will progress to an advanced or incurable state despite optimal therapy. A minority of women, 5-10%, will present with locally advanced or metastatic disease at diagnosis. Metastatic breast cancer is considered incurable, but treatable, with 70% of women dying of their disease within 5 years. The median life expectancy is 31 months.[13]

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

There are 4 subtypes of breast cancer as defined by gene expression profiling: luminal A, luminal B, her2-enriched, and basal-type.[14] These subtypes are simplified through classical immunohistochemistry for estrogen-receptor (ER)/progesterone-receptor (PR), and her2/neu (ERBB2), leading to hormone-receptor positive breast cancer, her2/neu amplified breast cancer, and triple-negative breast cancer. Each subtype is unique in its incidence, prognosis, and appropriate treatment algorithm.

Most breast cancers are hormonally driven. 65-70% of all breast cancers are ER positive (ER+) as detected by immunohistochemistry, making them potentially susceptible to endocrine therapies targeting this axis through systemic therapy.[15] Although most patients' disease will initially respond to endocrine therapy, eventually all patients will experience treatment failure. The selection and sequencing of hormone therapies are dependent factors that include: patient's preference, comorbidities of the patient, performance status (PS) involvement of vital organs, pace of the disease, and previous history of exposure to treatments in the adjuvant (curative) setting. The most effective treatment tends to be the one first employed, making the selection of such first-line therapy critical to a patients cancer journey. Second-line or later hormonal therapy without the addition of targeted therapy has led to response rates of <1%, and a PFS of < 3 months.[13] And although targeted agents have been shown to improve response rates and PFS, these improvements come with added toxicity and patient burden.

2.2 Accepted Clinical Practice

Advanced/metastatic breast cancer is considered an incurable condition. The goals of therapy focus on maintaining or improving patients' length of life and quality of life by controlling progression of the disease. Guidelines for ER+ her2/neu normal disease, strongly recommend hormonal therapy in the early lines of therapy given its favorable risk/benefit ratio, except in specific clinical scenarios, such as visceral crisis.[16] Hormonal therapies primarily include tamoxifen, a selective estrogen receptor modulator, aromatase inhibitors (e.g. anastrozole, letrozole, or exemestane), and fulvestrant, a selective estrogen receptor degrader. Of the three subtypes, only tamoxifen is effective in the treatment of ER+ breast cancer in pre-menopausal women. However, ovarian ablation or

chemical ovarian suppression is an acceptable adjunctive treatment to render pre-menopausal women post-menopausal.

Previously, sequencing of these therapies was guided by therapies received in the adjuvant setting (if applicable), disease-free interval and tolerability. Studies employing combination therapy, specifically with fulvestrant and anastrozole have been mixed: with one phase III randomized study unable to demonstrate superiority of the combination,[17] and another confirming the presence of both PFS and OS superiority.[18] The proportion of patients treated with prior hormonal therapy has been hypothesized as the cause of the disparity. Given the heterogeneity of results, combination therapy has not been widely adopted in Canada, but is an acceptable option.

More recently, the combination of the non-steroidal aromatase inhibitor letrozole with cyclin-dependent kinase (CDK) 4/6 inhibitors palbociclib or ribociclib has demonstrated PFS superiority over letrozole alone in the first-line setting for advanced or metastatic breast cancer.[19,20] This superiority was maintained both in patients who have been previously exposed to adjuvant hormonal therapy and those who had not. However, the PFS benefit must be weighed against the added toxicity of this combination therapy including frequent diagnostic phlebotomy, neutropenia, anemia, and fatigue.

On disease progression after first line therapy, hormonal therapeutic options include a change in mechanism of action (e.g. from an AI to tamoxifen or fulvestrant). The phase III CONFIRM trial[21] compared 2 dosing schedules of fulvestrant after previous hormonal therapy and demonstrated a statistically significant and clinically meaningful improvement in PFS and OS of a higher dose of fulvestrant, without sacrificing health-related quality of life . The PALOMA-3[22] trial randomized patients to either palbociclib and fulvestrant or fulvestrant alone and demonstrated an improvement in PFS for patients who had received prior hormonal therapy without previous exposure to a CDK4/6 inhibitor and was effective across all subgroups.

Conversely, concurrently the blocking the PI3K-AKT-mTOR pathway with everolimus and ER with the steroidal aromatase inhibitor exemestane demonstrated improvements in response rate, and PFS in ER+ ABC patients who demonstrated endocrine resistance.[13] However, everolimus added significant toxicity to exemestane, including pneumonitis, hyperglycemia, and oral ulceration, limiting the extent of its use.

2.3 Evidence-Based Considerations for a Funding Population

The requested funding population includes ER+ her2/neu normal advanced or metastatic breast cancer, presenting with previously hormone untreated disease. This population represents approximately 10% of all breast cancer diagnoses. Moreover, this funding request is limited to patients with non-visceral disease. Extrapolating from published studies, this may represent over 50% of previously untreated patients. The testing required for patient selection, ER and her2/neu testing by IHC is already mandatory and reflexive for all advanced and metastatic breast cancer and universally available across the country. The FALCON and FIRST trials included patients with performance status <3.

2.4 Other Patient Populations in Whom the Drug May Be Used

Based on the literature and clinical experience. Fulvestrant could also be considered for use after initial hormonal therapy, in combination with an AI in patients who have not been treated with hormonal therapy, in combination with a CDK4/6 inhibitor after previous hormonal therapy, and in patients with a performance status of 3. In all of these

situations, fulvestrant could be considered for use in all ER+ her2/neu normal breast cancer rather than limited to non-visceral disease.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, Rethink Breast Cancer (Rethink) and Canadian Breast Cancer Network (CBCN), provided input on the fulvestrant (Faslodex) submission for hormonal treatment of non-visceral locally advanced or metastatic HER-2 breast cancer in postmenopausal women, regardless of age, who have not been previously treated with endocrine therapy.

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

CBCN also conducted key informant interviews in July 2017 with two (2) Canadian metastatic breast cancer patients living with non-visceral disease that had direct experience with the treatment under review. A literature review of current studies and grey literature was also carried out by CBCN to identify issues and experiences that are commonly shared among many women living with breast cancer.

In addition, Rethink collected patient input from online surveys between June 30, 2017 to July 25, 2017. The survey also included questions directed to patients who had experience with fulvestrant. Potential responders were identified through the organizational mailing list, the Rethink Breast Cancer Young Women's Network, partner organizations as well as Facebook and Twitter. Forty-eight (48) patients completed the survey, of which 21 were from Canada (AB, BC, NS, ON, QB, and SK), 26 were from the US and 1 was from Italy. Of these patients, 45 have non-visceral locally advanced or metastatic breast cancer, 40 are post-menopausal and 6 have not been treated with endocrine therapy. Thirty-one (31) women have had treatment experience with fulvestrant and of those, 25 reported they had received fulvestrant in combination with other therapies.

Rethink asked patients through the survey if they would be willing to participate in an interview to elaborate on their experience. Twenty-two women were contacted and the eleven agreed were contacted by a Rethink Breast Cancer Staff for a one-on-one interview.

From a patient's perspective, managing a diagnosis of metastatic breast cancer is challenging, as current treatment options for metastatic breast cancer are only effective at prolonging progression-free disease, and most cases of advanced disease will progress and symptoms will worsen. Rethink and CBCN indicated that the many side effects of metastatic breast cancer represent a significant or debilitating impact (both physical and social) on patients' and caregivers' quality of life. Rethink and CBCN reported that bone pain, insomnia, fatigue, muscle weakness, shortness of breath, nausea, and loss of appetite were the most common symptoms experienced as a result of breast cancer. Respondents indicated that ability to work, ability to perform household chores, ability to travel and pursue personal hobbies and interests were impacted by breast cancer.

Respondents reported receiving a number of treatments, such as, palbociclib, letrozole, capecitabine, paclitaxel, zoledromate, exemestane, among others. 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 control the disease, (2) reduce symptoms, and (3) to improve on quality of life. Respondents who have experience with fulvestrant reported that the treatment helped to stabilize and control their disease. Respondents also commented on the ease of the injection and appreciated being able to schedule treatments that worked with their schedules, and that the side effects were minimal and tolerable.

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

3.1 Condition and Current Therapy Information

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

According to the 2012 Rethink and CBCN survey, current treatment options for Estrogen Receptor positive (ER-positive) metastatic breast cancer are only effective at prolonging progression-free disease, and most cases of advanced disease will progress and symptoms will worsen. Both Rethink and CBCN indicated that patients with a diagnosis of metastatic breast cancer understand the limitations of current treatment options, and seek to live their remaining months and years with the best possible quality of life that they can achieve.

The diagnosis of advanced breast cancer, as well as the treatments that are used, impact both the social and physical well-being of a patient thus impacting their quality of life. Both Rethink and CBCN reported from the 2012 survey how the disease presents itself through symptoms, how it progresses, and how it is experienced varies by patient. They also reported that many effects of metastatic breast cancer represent a significant or debilitating impact on patients' quality of life.

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

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

Rethink also reported from their 2017 patient survey in which 6 patients reported that they were diagnosed in 2017, 17 in 2016, 9 in 2015, 5 in 2014 and 10 in 2013 or earlier. Patients reported the symptoms they had experienced as a result of breast cancer: bone pain, reported by 76% of the 46 respondents, was the most common, followed by muscle weakness (50%), shortness of breath (41%), nausea (37%) and loss of appetite (33%). Patients also reported on how the symptoms associated with breast cancer have impacted their lives on a scale of 1 (no impact) to 5 (significant impact). Respondents indicated that the greatest impact was on their ability to work, followed by ability to exercise, ability to perform household chores and ability to travel. The following table illustrates the breakdown by percentage values for the responses that were reported.

Impact of breast cancer symptoms on different areas of life	1 - no impact	2	3	4	5 -significant impact	Average
Ability to work	16.67% 8	14.58% 7	18.75% 9	14.58% 7	35.42% 17	3.38 48
Ability to travel	18.75% 9	25.00% 12	33.33% 16	16.67% 8	6.25% 3	2.67 48
Ability to exercise	14.58% 7	18.75% 9	29.17% 14	27.08% 13	10.42% 5	3.00 48
Ability to perform household chores	16.67% 8	25.00% 12	29.17% 14	29.17% 14	0.00% 0	2.71 48
Ability to care for children	34.78% 16	21.74% 10	26.09% 12	8.70% 4	8.70% 4	2.35 46
Ability to fulfill family obligations	18.75% 9	29.17% 14	33.33% 16	16.67% 8	2.08% 1	2.54 48
Ability to spend time with family and friends	16.67% 8	33.33% 16	33.33% 16	14.58% 7	2.08% 1	2.52 48

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

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

Both Rethink and CBCN also reported from the 2012 survey 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 from the 2012 survey that other experiences identified by patients with breast cancer included: guilt, the feeling of being a burden on caregivers, fear of death, poor body image, not knowing what functionality will be lost, fear of impact of the cancer and the loss of a parent on children, not knowing what will happen to children, the loss of support of loved ones, martial stress/loss of fidelity and affection from husband.

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

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

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

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

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

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

1. Some patients felt they did not understand the wording of the question
2. Some patients felt they lacked capacity to respond to a hypothetical question of this nature.

Below were key responses from respondents from the 2012 survey:

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

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

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

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

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

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

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

CBCN and Rethink also reported from the 2012 survey on patients' access to local resources and support during treatment. It was reported that many patients living with cancer experience significant barriers and challenges around availability of health care services and quality childcare in their community.

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

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

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

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

Rethink reported responses from 48 respondents who provided information about the different treatments they had undergone since their diagnosis. Of which, 25 respondents also reported that they had disease progression with the treatment.

Treatments Received	n	Treatments Received	N
Palbociclib	26	Radiotherapy	2
Letrozole	17	Anastrozole	1
Capecitabine	13	Epirubicin	1
Paclitaxel	9	Lapatinib	1
Zoledromate	7	Pertuzumab	1
Exemestane	7	Leuprorelin	1
Denosumab	6	Trastuzumab emtansine	1
Tamoxifen	5	Fluorouracil	1
Everolimus	5	Ribociclib	1
Platinum agents	5	Enoxaparin sodium	1
Gemcitabine	5	Bazedoxifene	1
Trastuzumab	5	Taselisib	1
Docetaxel	4	Pembrolizumab	1
Doxorubicin	4	Vinorelbine	1
Cyclophosphamide	3	Craniotomy	1
Goserelin	3	Dasatinib	1
Eribulin	2	Unspecified hormone blockers	1
Aluminum-bound paclitaxel	2	Unspecified aromatase inhibitor	1

Rethink reported from the 2017 survey that fatigue was the most commonly reported side effect from the treatments listed above (92% of the 48 respondents), followed by joint pain (69%), muscle pain (52%), back pain (48%), insomnia (48%), diarrhoea (42%), constipation (42%) and nausea (38%). Rethink also asked patients in the same survey about difficulties accessing cancer treatment. Thirty four (34) of the 48 respondents (71%) reported none. Patients did report that they faced financial challenges as a result of their cancer treatment, 48% faced financial challenges as a result of drug costs, 42% due to lost income from work absences, 27% due to travel costs and 21% due to parking costs. The remaining 30% of patients did not report any financial challenges.

3.1.3 Impact of Metastatic Breast Cancer and Current Therapy on Caregivers

Caregiver experience was not provided by CBCN and Rethink.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Fulvestrant

According to the 2012 survey, both CBCN and Rethink reported on the impact and value to patients with the new treatment under review. In particular, it was very important for patients to have quality of life when receiving treatment for metastatic disease. Respondents reported the importance to have the energy to attend children's activities and to spend time with family and friends.

CBCN reported that patients have an expectation that fulvestrant will extend progression free survival and allow them to live a better quality of life than if they were to receive

chemotherapy or other hormonal therapies with more significant toxicity profiles. CBCN believes that these values aligns with the results of Phase III Falcon Trial.

CBCN reports that by delaying the progression of disease, treatments can relive cancer-related symptoms and improve patients' quality of life. Living with minimal side effects, patients are able to reduce the impact of cancer on their ability to care for children and dependents, continue with their employment and earn an 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.

Patients interviewed by CBCN stressed the importance of having diverse treatment options available to them in order to avoid having to turn to chemotherapy as a treatment option.

Rethink asked patients to evaluate the important outcomes for their breast cancer treatment on a scale of 1 (not important) to 5 (very important). From the results, listed in the table below, all of the listed outcomes were considered important with an average score over 4. Outcomes such as life controlling disease and ensuring longer survival were rated more important than reducing symptoms and managing side effects. Rethink suggests that patients and patient values prioritize long term health outcomes over short term relief.

Impact of outcome for breast cancer treatment	1 - not important	2	3	4	5 – very important	Average
Controlling disease	6.25% 3	0.00% 0	0.00% 0	0.00% 0	93.75% 45	4.75 48
Reducing symptoms	4.17% 2	6.25% 3	14.58% 7	18.75% 9	56.25% 27	4.17 48
Maintaining quality of life	4.17% 2	0.00% 0	6.25% 3	6.25% 3	83.33% 40	4.65 48
Managing side effects	2.08% 1	0.00% 0	16.67% 8	27.08% 13	54.17% 26	4.31 48
Achieving NED (no evidence of disease)	4.17% 2	4.17% 2	16.67% 8	14.58% 7	60.42% 29	4.23 48
Ensuring longer survival	6.25% 3	0.00% 0	0.00% 0	2.08% 1	91.67% 44	4.73 48

Rethink also asked respondents if they would be willing to tolerate new side effects from new drugs in exchange for reduced disease progression for a short period of time, or increased overall survival time. On a scale of 1 (will not tolerate side effects) to 10 (will tolerate significant side effects), respondents gave an average score of 6.2 for their willingness to tolerate new side effects for a short period of reduced disease progression and an average score of 7.9 for their willingness to tolerate side effects for an increased overall survival time, again suggesting that patient values prioritize long-term health outcomes.

3.2.2 Patient Experiences with fulvestrant

CBCN was able to find two Canadian patients with experience with fulvestrant. The first patient had been on treatment since January 2017 (7 months on fulvestrant), and is living with non-visceral metastatic disease. The first respondent is female and is accessing fulvestrant as the first treatment for her metastatic breast cancer at an Ontario Cancer Centre. The second respondent has been on treatment since October 2016 (10 months on

fulvestrant) and living with non-visceral metastatic disease. She is accessing treatment through private insurance in Ontario and has had previous treatment with capecitabine, goserelin, letrozole, exemestane and everolimus. The interview responses from these two respondents are noted below.

Rethink had 31 respondents who reported receiving fulvestrant of which 25 respondents received fulvestrant in combination with other therapies. Of these respondents, 13% were treated for 3 months or less, 29% were treated for 3-6 months, 20% were treated for 6-12 months and 39% were treated for more than one year. Interviews of 11 respondents were also conducted by Rethink Breast Cancer though number of patients who received fulvestrant was not reported.

Respondents responding to the Rethink survey were asked to rate the effectiveness of fulvestrant on improving life with breast cancer on a scale of 1 (not at all effective) to 5 (very effective). The responses noted in the table below suggest that respondents consider fulvestrant as moderately effective for improving disease progression, drug side effects and quality of life.

Effectiveness of Faslodex on improving living with breast cancer	1 - not at all effective	2	3	4	5 – very effective	Average
Disease progression	22.58% 7	3.23% 1	9.68% 3	19.35% 6	45.16% 14	3.61 31
Metastatic cancer symptoms	2.90% 4	6.45% 2	32.26% 10	25.81% 8	22.58% 7	3.39 31
Drug side effects	6.45% 2	6.45% 2	29.03% 9	29.03% 9	29.03% 9	3.68 31
Quality of life	6.45% 2	12.90% 4	12.90% 4	29.03% 9	38.71% 12	3.81 31
NED (no evidence of disease)	43.33% 13	6.67% 2	20.00% 6	10.00% 3	20.00% 6	2.57 30

Below were comments made by respondents interviewed by Rethink to help illustrate their experiences with fulvestrant:

- *"Other than being really tired I am not having any side-effects. It's been positive and allows me to maintain a good quality of life. I am able to work and exercise. There isn't anything I can't do!"*
- *"It's been amazing with my quality of life. I was at a bad point when I started it, and it really saved my life by allowing me to live my life."*

Respondents interviewed by CBCN also reported on the impact of the treatment on the disease. Both respondents expressed personal satisfaction with the treatment and noted that their oncologists are pleased with fulvestrant controlling their disease. Both respondents discussed their ability to live life productively, with an excellent quality of life.

- "*My doctor is very happy with the results! It seems like the treatment is controlling the cancer and has given me a much better outlook. I have regained my mobility and my ability to be productive. I can actually do daily tasks again, like cleaning the house, and even just moving around is so much easier now, when I've been basically living in pain all this time!"-Patient 1*

- *"I had my last scan in April and the fulvestrant still seems to be working for me. My oncologist is impressed because this is the first time, with all of the treatments that I have been on, that my tumors have actually begun to shrink! "-Patient 2*

In addition, both respondents reported on assessing the risks associated with the treatment. Respondents were well aware of the possible risks of fulvestrant and were made aware that all patients can respond differently to side effects. Both respondents interviewed found the side effects to be minimal and manageable.

- *"If I knew it was controlling the cancer, I would deal with it all, but I'm just so relieved that I don't have to even worry about that now."-Patient 1*
- *"Some of the other treatments I have been on have been brutal with the side effects-just extremely painful and uncomfortable. I haven't had any issues with this one and I'm so grateful that it isn't a problem"-Patient 2*

When asked about alternatives, one of the respondent interviewed was uncertain about what her other treatment options may be, and the second respondent mentioned that without this treatment she would only be left with chemotherapy as an alternative treatment.

- *"After this, it will probably be chemo, which is way worse than anything else. This is what really frustrates me-there are just not enough other options for hormone receptor positive cancers, so I'm hoping this treatment will last as long as possible for me!"*-Patient 2

Patient respondents for the Rethink survey generally regarded the side effects associated with fulvestrant as tolerable. On a scale of 1 (completely tolerable) to 5 (completely intolerable), the average rating was 2.1 and 48% of respondents answered with the lowest possible rating indicating that the side effects were completely tolerable.

Rating	Responses
1	48.39% 15
2	16.13% 5
3	22.58% 7
4	3.23% 1
5	9.68% 3

Below were comments from the patient interviews conducted by Rethink regarding their experience with side effects fulvestrant:

- "*Overall if I compare it to chemo and IV it's way less side-effects. Out of all the drugs I've tried there are way less side-effects. No hot flashes, no neuropathy, no night sweats.*"
- "*I know there is always side-effects with medication and I am just putting up with it. It's a lot more tolerable than the last oral chemo I was on. That drug affected my skin and energy.*"
- "*I have had no negative effects at all. This has been really positive for me. Other drugs make me sick, but this one has been a miracle. No side effects."*
- *"I was bent over in so much pain and within two weeks or less, all of my pain was gone with Faslodex."*

Respondents who were interviewed by CBCN shared that their side effects were minimal to non-existent and that their quality of life, including productivity and ability to regain mobility and perform daily functioning had improved on fulvestrant.

- *"Nausea, headaches and joint pain are the worst possible symptoms for me. I'm very relieved that I have not had to deal with any of those symptoms while on this treatment. The worst I've had is some soreness at my hips-but it subsides after a little while and I don't have to deal with anything else!"*- Patient 1

- *With all the treatments I have been on, I'm very used to side effects. Hot flashes, diarrhea, joint pain, nausea, hair loss, nerve pain and canker sores were some of the worst ones that I have experienced with other treatments. Compared to those, this has been a cakewalk! I still do get some hot flashes, but it is very minimal compared to the other treatments which seemed to make them worse and really I think that might just be more me than the medication!"* –Patient 2

Rethink also reported on several patient comments on their experience with the administration of fulvestrant, which included the following:

- "*Side-effects were almost none. The injections were no where near as bad as people think they are*."
- "*The injection site is sore for a few days and bruised. It's completely tolerable*."
- "*I am really lucky - the shots don't bother me*."
- "*I get the injections at the hospital and it's easy. The injection hurts but it's convenient*."

Respondents from Rethink had mixed opinions about where and how they wanted to receive fulvestrant. Patient comments included:

- "*I am glad I didn't have to administer the injection myself or put that on a family member. I appreciate being in a hospital where they know what they are doing*."
- "*I have two daughters at home who can administer it. They give it to me and it is great to not have to go to the hospital so it's very convenient*."

Respondents interviewed by CBCN also commented on the ease of the injection and appreciated being able to schedule treatment in their lives.

- *"Some people have difficulty with needles but I'm fine with it. I just take an Ibuprofen before my appointments. My quality of life is good and I don't feel tied to a treatment. I'm so used to taking pills and this is so much better. I'm really hoping to keep staying on this*!"-Patient 2

In commenting on the social and financial impact of the treatment, respondents interviewed by CBCN did not discuss the financial impact of the treatment, but did discuss the impact that access to fulvestrant had on their quality of life and ability to be productive.

- *"I'd rate my quality of life with fulvestrant as very effective and highly satisfactory! I think all patients should be able to access this and I think it's well worth it for the provinces to reimburse this treatment"*-Patient 1

"Having access to this treatment means a much better chance for a decent quality of life. It is another option away from chemotherapy which means a lot to me and I just hope that more people can have access to this treatment. It makes your life so much easier without being tied to a daily schedule to remember to take a pill. With access to more treatment options, the longer you have to enjoy your life, the better your life actually is."-Patient 2

3.3 Additional Information

No additional information was provided by CBCN or Rethink Breast Cancer

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

Input was obtained from five of nine provinces (Ministries of Health and/or cancer agencies) and the federal drug plan participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Clarity on the eligible patient group
- Advice on sequencing of current treatments and place in therapy

Economic factors:

- Requires nursing to administer intramuscular injections monthly

Please see below for more details.

4.1 Factors Related to Comparators

Current endocrine therapies for locally advanced or metastatic endocrine receptor positive breast cancer in postmenopausal women include aromatase inhibitors or tamoxifen. PAG noted that anastrozole in the comparator arm in the FALCON trial is an appropriate comparator.

At the time of this PAG input, palbociclib is not yet funded in any province. However, PAG is seeking whether there is information comparing palbociclib plus letrozole to fulvestrant.

4.2 Factors Related to Patient Population

PAG noted that patients in the FALCON trial are postmenopausal women with locally advanced or metastatic ER+, PR+ or PR-, and HER2 negative, breast cancer who are endocrine therapy-naïve. However, the funding request is for a subgroup of patients with non-visceral disease and PAG is seeking clarity on the eligible patients. PAG is also seeking clarity on whether patients treated with endocrine therapy in the adjuvant setting would be eligible for treatment with fulvestrant for locally advanced or metastatic disease.

PAG indicated that there would be requests for the use of fulvestrant in combination with palbociclib based on the publication of PALOMA-3 trial results demonstrating fulvestrant plus palbociclib is superior in terms of PFS compares to fulvestrant alone. Noting that fulvestrant plus palbociclib would be out of scope of this review, PAG is seeking information from the manufacturers of fulvestrant and palbociclib on when a submission for funding consideration of the combination would be available.

PAG is seeking guidance on the appropriate sequencing of aromatase inhibitors, targeted therapies and fulvestrant. There are patients who have received treatment with palbociclib or fulvestrant from clinical trials or manufacturer compassionate access programs and require further treatment.

PAG is also seeking guidance on the use of fulvestrant in patients who have completed chemotherapy and may benefit on a "maintenance" hormone regimen after maximal chemotherapy response.

4.3 Factors Related to Dosing

Fulvestrant is available as 250mg pre-filled syringes. Pharmacy preparation is not required and there is no wastage concerns as the dose is 500mg given as two separate injections.

4.4 Factors Related to Implementation Costs

Fulvestrant requires nursing resources to administer the intramuscular injection. Patients would need monthly treatment visits, which requires incremental resources over patients who receive oral endocrine therapy.

4.5 Factors Related to Health System

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

4.6 Factors Related to Manufacturer

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One clinician input was provided on fulvestrant for locally advanced or metastatic breast cancer. The input was provided as a joint submission from three oncologists who are members of Cancer Care Ontario (CCO) Breast Site Group. Their input is summarized below.

Overall, clinicians providing input note that hormone receptor positive advanced breast cancer is prevalent in post-menopausal women. Based on trial evidence, clinicians state that fulvestrant is more effective and has lower toxicity than anastrozole in patients with locally advanced or metastatic breast cancer. However, the survival benefit is reported to be non-significant in patients with visceral disease and those with a history of prior chemotherapy. Therefore, first-line therapy with fulvestrant would be appropriate in low- or intermediate-risk advanced or metastatic disease with good prognosis (e.g., non-visceral disease), high-risk patients with comorbidities who are not eligible for combination targeted therapies. The drug would be used as an alternative to aromatase inhibitors (letrozole) + CDK4/6 inhibitors (palbociclib and ribociclib), and in patients for whom CDK4/6 inhibitor is not indicated, e.g., those who are unable to tolerate CDK4/6 inhibitor, or those who have comorbidities. One clinician expressed concerns over considering fulvestrant as a first line treatment option for hormone-receptor positive metastatic breast cancer, due to uncertainties around clinical and safety advantages of fulvestrant over existing alternative treatments.

Please see below for details from the clinician input.

5.1 Current Treatment(s) for Metastatic Breast Cancer

The oncologists providing input identified that the current standard treatments for locally advanced or metastatic breast cancer include:

- A combination of letrozole and palbociclib (although not yet publicly funded in any provinces at the time of this input)
- A combination of letrozole and ribociclib (available through enrolling in the expanded access trials);
- Aromatase inhibitors; and
- Chemotherapy, in patients for whom endocrine therapy is not appropriate.

5.2 Eligible Patient Population

The clinicians providing input noted that hormone receptor positive advanced breast cancer is prevalent in post-menopausal women. The clinicians providing input noted that most clinicians would not prescribe fulvestrant in the first-line setting and suggested that this drug may be regarded as an alternative to letrozole + palbociclib in patients who do not want to be treated with a CDK4/6 inhibitor.

5.3 Identify Key Benefits and Harms with Fulvestrant

Referring to the results of the FALCON study, the clinicians providing input noted that, when comparing to anastrozole, fulvestrant resulted in a greater PFS improvement and lower drug toxicity. However, in patients with visceral disease, PFS rates were similar between the two treatment groups. A pre-

specified subgroup analysis of the trial data showed that patients who received prior chemotherapy did not benefit from fulvestrant.

The drug is administered through intra-muscular injection.

5.4 Advantages of Fulvestrant Over Current Treatments

Referring to the discussion section of FALCON study, the clinicians providing input noted that fulvestrant could be considered as a lower toxicity option for first-line therapy in patients with locally advanced or metastatic breast cancer. They stated that the drug was favourable in patients who have a low- or intermediate-risk disease with good prognosis (e.g., non-visceral disease), patients with high-risk disease who have comorbidities limiting the use of combination targeted therapies, patients who cannot afford a CDK4 or CDK6 inhibitor, or in countries where CDK4 or CDK6 inhibitors have not been approved by regulatory authorities**.**

5.5 Sequencing and Priority of Treatments with Fulvestrant

Fulvestrant would be used as an alternative to an aromatase inhibitor + CDK4/6 inhibitors, and in patients for whom CDK4/6 inhibitor is not indicated, e.g., those who are unable to tolerate CDK4/6 inhibitor, or those who have comorbidities.

There is potential for expanding the use of fulvestrant as an option for second-line therapy after CDK4/6 agents**.**

5.6 Companion Diagnostic Testing

The joint clinical input document identified estrogen and progesterone receptor testing as the standard of care for patients with locally advanced or metastatic breast cancer.

5.7 Additional Information

One clinician commented: “Respectfully: I am not as impressed by the FALCON trial results. I actually do not see a toxicity or clinically meaningful advantage to advocating this as a funded option in the setting of first line therapy for HR positive metastatic breast cancer. Meaningful toxicities were pretty well equivalent and we do have oral options. There is also no significant difference in adherence. In addition, implementation of an injection program as first line therapy could be problematic and have an impact on drug and administrative costs. I think we should be “raising the bar” for therapies and focusing on making truly new therapies available.”

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of fulvestrant for hormonal treatment of non-visceral locally advanced or metastatic HER2- breast cancer in postmenopausal women, regardless of age, who have not been previously treated with endocrine therapy. (See Table 1 in Section 6.2.1 for outcomes of interest).

The following supplemental issue was identified as relevant to the pCODR review of fulvestrant for hormonal treatment of non-visceral locally advanced or metastatic HER2- breast cancer in postmenopausal women, regardless of age, who have not been previously treated with endocrine therapy (see Section 7):

- Critical appraisal of the manufacturer-submitted network meta-analysis (NMA) comparing fulvestrant to palbociclib plus letrozole in the non-visceral population.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 1. Selection Criteria

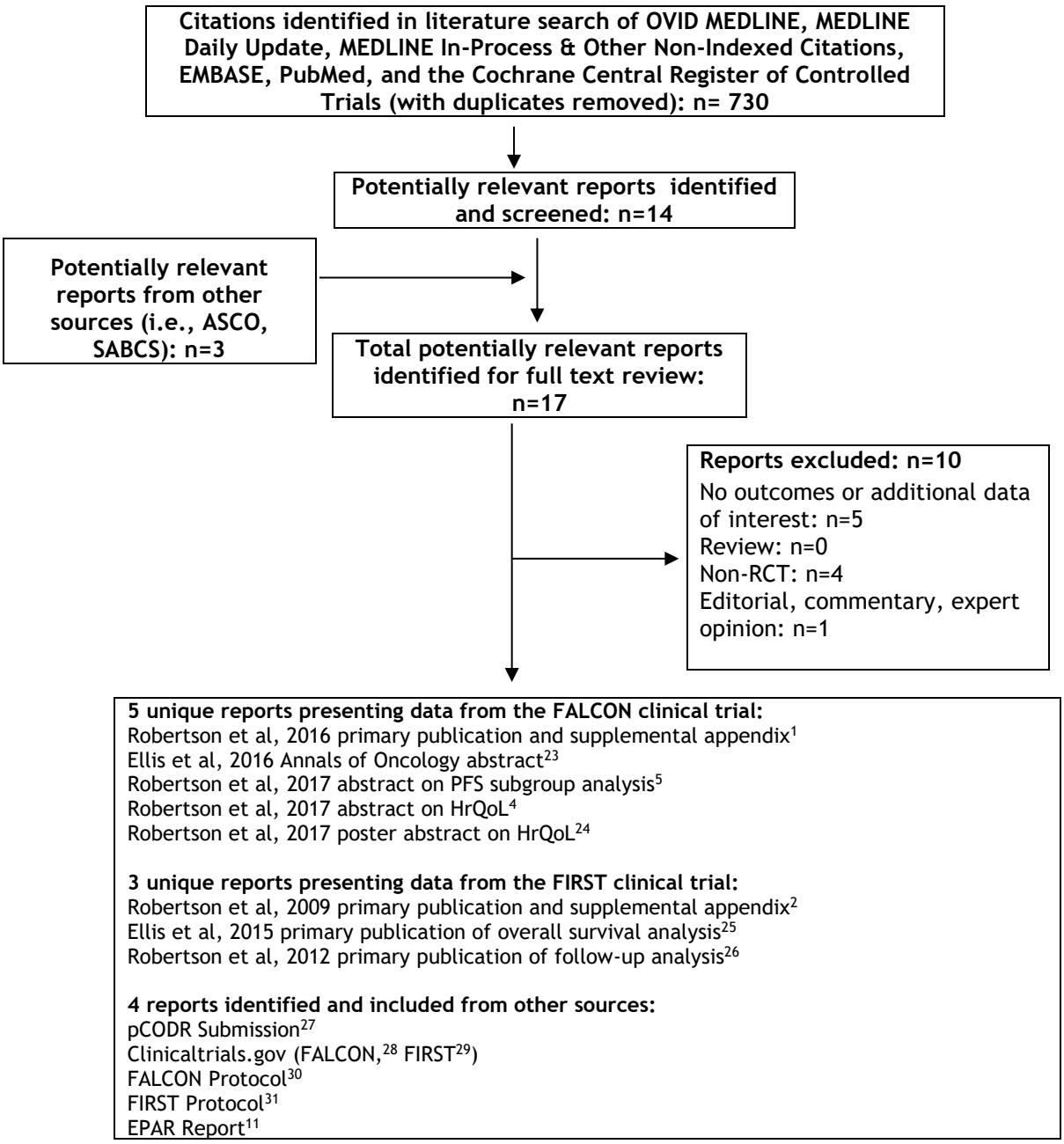
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of fulvestrant should be included.	Post-menopausal women with non-visceral locally advanced or metastatic HER2- breast cancer who have not been previously treated with endocrine therapy <u>Subgroups:</u> • Site of disease (e.g., non-visceral) • ER/PR Status • Locally advanced or metastatic disease	Fulvestrant (500 mg)	Endocrine therapy: • Aromatase inhibitors (e.g., letrozole, anastrozole, exemestane) • Selective estrogen receptor modulators (e.g., tamoxifen) Palbociclib + Letrozole	<u>Efficacy</u> • **OS** • **PFS** • **HrQoL** • ORR • DoR • CBR <u>Safety</u> • **AEs** • SAEs • WDAEs • Local injection reactions (e.g., pruritus, urticaria) • Hematoma • Hepatic failure
Abbreviations: AE=adverse events; **CBR=**clinical benefit rate; **DoR**=duration of response; **ER/PR**=estrogen receptor/progesterone receptor; **HER2=**human epidermal growth factor receptor 2; **HrQoL**=Health-related quality of life; **RCT=**randomized controlled trial; **ORR**=objective response rate; **SAE**=serious adverse events; **WDAE**=withdrawals due to adverse events **Notes:*** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).				

6.3 Results

6.3.1 Literature Search Results

Of the 17 potentially relevant reports identified, seven studies were included in the pCODR systematic review and ten studies were excluded. Studies were excluded because they: did not report outcomes or additional data of interest; not randomized controlled trials; or editorial/commentary/expert opinion.

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of Studies



Note: Additional data related to the FALCON and FIRST studies were also obtained through requests to the Submitter by pCODR.[3]

6.3.2 Summary of Included Studies

Two clinical trials, the FALCON and FIRST trials,[1,2] met the inclusion criteria for this systematic review. The key characteristics of these trials are summarized in Table 2 and specific features of trial quality are summarized in Table 3.

6.3.2.1 Detailed Trial Characteristics

Table 2: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NCT01602380 FALCON Double-blind phase III RCT Patient Enrollment: 17 October 2012 to 11 July 2014 Data cut-off Date: 11 April 2016 Estimated Study Completion Date: 12 February 2018[28] Randomized = 462 Treated = 460[1] 113 academic hospitals and community centres in 20 countries Funding by: AstraZeneca	Key Inclusion Criteria:[28] Histological confirmation of breast cancer in post-menopausal women, fulling one of: • Prior bilateral oophorectomy • Age >60 years • Age < 60 years and amenorrheic for 12+ months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and FSH and oestradiol in the postmenopausal range Positive hormone receptor status (ER +ve and/or PgR +ve) of primary or metastatic tumour tissue based on local laboratory assessment EITHER locally advanced disease (1 line of chemotherapy allowed only if remain unsuitable for therapy of curative intent) OR Metastatic disease (1 line of chemotherapy for breast cancer allowed only if subsequent evidence of further progressive disease) WHO performance status 0-2 One or more measurable or non-measurable lesion Key Exclusion Criteria:[28] Presence of life-threatening metastatic disease Any of: • Extensive hepatic involvement • Involving brain or meninges • Symptomatic pulmonary lymph spread Prior systemic therapy for breast cancer other than one line of cytotoxic chemotherapy (the last dose of chemotherapy must have been received more than 28 days prior to randomisation) Radiation therapy if not completed within 28 days prior to randomisation (with the exception of radiotherapy given for control of bone pain, started prior to randomisation). Prior hormonal treatment for breast cancer Discrete lung metastases are acceptable if respiratory function is not significantly compromised Current or prior malignancy within previous 3 years (other than breast cancer or adequately treated basal cell or squamous cell carcinoma of the skin or in situ carcinoma of the cervix)	Intervention: Fulvestrant Comparator: Anastrozole Fulvestrant 500 mg (plus daily anastrozole placebo) was administered on days 0, 14 (±3), 28 (±3), and every 28 (±3) days thereafter as two 5 mL intramuscular injections at each visits. Anastrozole 1 mg orally daily (plus fulvestrant placebo on days 0, 14, 28, and every 28 days thereafter) was administered once daily as a single tablet. Treatment continued until objective disease progression or other criteria for discontinuation were met in terms of adverse events, protocol non-adherence, or patient's decision to withdraw.	Primary: PFS Secondary:[28] OS, ORR, DoR, EDoR, CBR, DoCB, EDoCB, HrQoL, safety

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NCT00274469 FIRST Open-label phase II RCT Patient Enrollment: 6 February 2006 to 11 July 2007[29] Data cut-off Date: 10 January 2008[29] Primary Study Completion Date: January 2008[29] Randomized = 205 Treated = 204[2] 62 centers in 9 countries Funding by: AstraZeneca	<u>Key Inclusion Criteria:</u> Post-menopausal women with ER + and/or PgR + locally advanced or metastatic breast cancer who were not amenable to therapy of curative intent Prior endocrine therapy for advanced disease was not permitted, but patients could have received adjuvant endocrine therapy for early disease, provided it was completed more than 12 months before random assignment WHO performance status 0-2 Measurable disease per modified RECIST criteria, or at least one bone lesion with a lytic component <u>Key Exclusion Criteria:</u> Presence of life-threatening metastases Current or prior malignancy (except breast cancer or adequately treated skin cancer or in situ carcinoma of the cervix) Treatment with a non-approved or experimental drug in the 4 weeks before being randomly assigned Abnormal laboratory test values History of bleeding diatheses Long-term anticoagulant therapy Hypersensitivity to excipients of fulvestrant, AIs, or castor oil Any severe concomitant conditions	Intervention: Fulvestrant Comparator: Anastrozole Fulvestrant 500 mg (two 250 mg intramuscular injections) on day 0, 14±3, 28±3, and every 28±3 days thereafter Anastrozole (1 mg/day orally), dispensed once every 28 ±7 days Patients received treatment until they experienced disease progression or another event requiring discontinuation	<u>Primary:</u> CBR <u>Secondary:</u> ORR, TTP, DoR, DoCB, safety

Abbreviations: +ve = positive, **CBR** = clinical benefit rate, **EDoCB** = expected duration of clinical benefit, **EDoR** = expected duration of response, **ER** = estrogen receptor, **DoCB** = duration of clinical benefit, **DoR** = duration of response, **FSH** = follicle-stimulating hormone, **HrQoL** = health-related quality of life, **mg** = milligram, **NR** = not reported, **ORR** = objective response rate, **OS** = overall survival, **PFS** = progression-free survival, **PgR** = progesterone receptor, **RCT** = randomized controlled trial, **RECIST** = Response Evaluation Criteria in Solid Tumors, **TTP** = time to progression, **WHO** = World Health Organization

Table 3: Select quality characteristics of included studies of fulvestrant in patients with locally advanced or metastatic breast cancer

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
FALCON	Fulvestrant vs. Anastrozole	PFS [C]	450 patients to achieve 306 progression events to provide 90% power for a HR=0.69 at a 5% two-sided	230 vs. 232	IVRS/IWRS, blocked scheme[A]	Yes	Double-blind, double-dummy	Yes	Yes[B]	No	Yes

			statistical significance level[1]								
FIRST	Fulvestrant vs. Anastrozole	CBR	100 patients per treatment group to provide 80% power to rule out an absolute deficiency of 20% in CBR for fulvestrant with a two-sided 95%CI[2]	102 vs. 103	Stratified by centre using randomized schemes[31]	No	Open-label study Response determined by blinded, independent review	Yes	Yes	No	Yes

Abbreviations: CBR = clinical benefit rate, **CI** = confidence interval, **HR** = hazard ratio, **IVRS/IWRS** = interactive voice response system/interactive web response system, **PFS** = progression-free survival
Notes: [A]Patients were stratified at randomisation according to locally advanced or metastatic breast cancer; previous or no previous treatment with chemotherapy for locally advanced or metastatic breast cancer; and measurable or non-measurable disease
[B]Interim survival analysis was performed at the same time as the primary analysis of PFS and a subsequent survival analysis was planned to be conducted at 50% maturity[30]
[C]The smallest treatment difference that would be statistically significant was a PFS HR=0.80, this translates to approximately a 3.3-month median difference, assuming proportional hazards and an exponential distribution[11]

a) Trials

FALCON and FIRST trials were both international, multi-centered RCTs. FIRST, which preceded FALCON, was a phase II non-inferiority trial evaluating the efficacy and safety of fulvestrant compared with anastrozole as first-line endocrine therapy for advanced hormone receptor-positive breast cancer in postmenopausal women. FALCON, a double-blind trial, was designed to determine whether fulvestrant was superior to anastrozole, in terms of prolonging progression-free survival (PFS), among postmenopausal patients who had not received previous endocrine therapy. The trials compared identical active interventions and schedules, assessed similar outcomes, and enrolled patients based on very similar eligibility criteria (refer to Table 2 for a complete list of criteria) that included the following:

- Post-menopausal women
- Hormone receptor positive status
- Locally advanced or metastatic breast cancer who were not amenable to therapy of curative intent
- WHO performance status 0-2

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

- FALCON:
    - No prior systemic therapy for breast cancer other than one line of cytotoxic chemotherapy (i.e. prior hormonal treatment for breast cancer)[30]
    - Include a placebo-control and double-blinding
    - Stratified randomization by locally advanced or metastatic breast cancer, prior chemotherapy, and measurable disease at baseline
- FIRST
    - Included patients who received adjuvant endocrine therapy for early disease, provided it was completed more than 12 months before random assignment
    - Open-label design
    - Stratified randomization by centre only

FALCON

FALCON enrolled 462 patients between October 2012 and July 2014 at 113 sites from 20 countries, including Canada with 6 sites in the three provinces of British Columbia, Ontario, and Quebec.

Patients were randomized in a 1:1 ratio to the fulvestrant or anastrozole treatment groups, respectively, using central randomization methods. The randomization procedure was stratified by disease (locally advanced or metastatic), prior chemotherapy (yes/no), and measurable (or non-measurable) disease. Study visits occurred at screening, randomisation, day 14, every 4 weeks from week 4 to week 24, and every 12 weeks thereafter until disease progression. The trial was double-blind, therefore patients and investigators were blinded to assigned treatment. Safety and tolerability were assessed at every study visit and up to 8 weeks after the last treatment injection. Health-related quality of life (HrQoL) questionnaires were administered at baseline and every 3 months thereafter; after disease progression or treatment discontinuation, questionnaires were administered every 6 months until the final overall survival analysis.

The primary outcome of the trial was investigator-assessed PFS, defined as RECIST version 1.1, or surgery or radiotherapy for worsening of disease, or death from any cause. The secondary outcomes of the trial included the following: ORR (best overall response of either complete response or partial response in patients with measurable disease at baseline, duration of response (DoR), expected duration of response (EDoR), clinical benefit rate (CBR) which includes best overall response of complete response, partial response, or stable disease ≥ 24 weeks), duration of clinical benefit (DoCB), expected duration of clinical benefit (EDoCB), and overall survival (OS) defined as the time from randomisation until death by any cause. Health-related quality of life (HrQoL) was assessed using the Trial Outcome Index derived from the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) questionnaire and FACT-B total score. Safety included adverse events (graded according to Common Terminology Criteria for Adverse Events [CTCAE], version 4.0), serious adverse events, discontinuations because of adverse events, deaths because of adverse events, and predefined adverse events of special interest (joint disorders and back pain).

The primary analysis was completed in the intent-to-treat population and safety outcomes were assessed in all patients who received at least one dose of randomised treatment. PFS assessment for fulvestrant versus anastrozole was done using a stratified log-rank test at a two-sided 5% significance level. For the survival analysis, an interim analysis was conducted at the same time as the PFS analysis. A multiple testing procedure to strongly control type-I error at the overall alpha level was implemented and used to test the key secondary endpoints with an alpha-exhaustive recycling strategy.[11] Besides secondary endpoints of OS and ORR (pre-defined order using a weighted proportion of alpha such that initially α=2% is allocated to OS and α=2% is allocated to ORR), other secondary endpoints were not protected for multiplicity.[11] Refer to Table 3 for a more detailed summary of statistical and sample size considerations in the trial.

Subgroup analyses were conducted as sensitivity analyses; subgroup hypotheses were not reported and there was no formal procedure for controlling error rates. Subgroup analysis was completed for PFS data for the following baseline covariates: estrogen receptor-positive and progesterone receptor-positive (yes or no), metastatic disease (yes or no), concomitant use of bisphosphonates (yes or no), measurable disease (yes or no), previous chemotherapy for locally advanced or metastatic breast cancer (yes or no), geographic region, previous systemic estrogen containing hormone replacement therapy (yes or no), and visceral disease (yes or no). Of note, during changes to the planned analyses, visceral

disease was included as a subgroup analysis for PFS and as a covariate used for the Cox regression sensitivity analysis of PFS.[11]

One protocol amendment was made at the start of recruitment of patients in the FALCON study; this amendment was minor in nature (e.g., clarifications as well as specifications related to the exclusion criteria) and made at the time recruitment started.[11] There was one post-unblinding change made to the planned analyses which was the inclusion of an additional sensitivity analysis of PFS which fitted stratification factors derived from eCRF data (rather than the IVRS system).[11]

AstraZeneca funded the trial and was involved in study design, reviewing and interpreting the data, and writing the manuscript.

FIRST

FIRST enrolled 205 patients, between February 2006 and July 2007, at 62 centers from 9 countries, not including Canada.

Patients were randomized in a 1:1 ratio to the fulvestrant or anastrozole treatment groups, respectively. The randomization procedure was stratified by centre. Tumour assessment (clinical and radiologic) occurred at screening visit and then every 12 ±2 weeks following random assignment until disease progression. The trial was open-label, therefore patients and investigators were not blinded to assigned treatment. Scans for all patients were collated and reviewed in a blinded manner by an independent radiologist working for a contract services organization. Other post hoc analyses were performed by the Biostatistics department at AstraZeneca.[26] Safety with respect to laboratory tests and incidence of adverse events were recorded throughout the study. HrQoL was not assessed in the FIRST study. A further analysis of data during the follow-up phase was planned to be performed when approximately 75% of patients were no longer receiving randomized study treatment; OS analysis was to be performed when approximately 65% of patients had died.[31] Authors noted as this was a phase II trial, no further adjustments were made for multiple testing.[26]

The primary outcome of the trial was CBR, defined as the proportion of all randomly assigned patients who had a best overall response of a complete response, a partial response, or stable disease for at least 24 weeks. The secondary outcomes of the trial included the following: ORR, TTP, DoCB, and DoR.

The primary analysis compared CBR in the two groups using logistic regression model and was to occur 6 months after the last patient had been randomly assigned. Refer to Table 3 for a more detailed summary of statistical and sample size considerations in the trial.

The follow-up analysis to assess OS utilized the log-rank test and a statistical significant level of 0.05 was used to indicate a difference in OS between the treatment groups.[25] Exploratory subgroup analyses were conducted for pre-specified patient subgroups of : <65 years of age versus ≥ 65 years of age; not ER+/PgR+ versus EG+/PgR+; no visceral involvement versus visceral involvement; no previous chemotherapy versus previous adjuvant chemotherapy; no measurable disease versus measurable disease; and no previous endocrine therapy versus previous endocrine therapy.[25]

One protocol amendment was made at the start of patient recruitment in the FIRST study which included clarifications and additional wording/categorization. Three amendments for follow-up analyses in the FIRST study were conducted, 1) follow-up analysis for progression after 75% of patients had failed therapy;[26] 2) follow-up analysis of OS;[25] and 3) follow-up analysis of OS at 65% rather than 75% maturity given the significant decline in rate of death which was observed in the later stages of the OS follow-up. The first follow-up analysis amendment was conducted to allow for more meaningful interpretation of the

secondary endpoint of TTP. Based on a statistically significant benefit in TTP for fulvestrant, the follow-up analysis was amended to investigate whether the benefit in TTP translated to an OS benefit.[3]

AstraZeneca funded the trial, however, limited information is known regarding the extent of the funder's role in the conduct of the trial (e.g., study design, treatment administration, data collection, database access.

b) Populations

The baseline characteristics of patients in the FALCON and FIRST trials are summarized in Table 4. In general, the distributions of patient characteristics appeared similar in the trials, with the exception of higher proportions with locally advanced disease in FIRST; previous locally advanced or metastatic chemotherapy in FALCON; and previous adjuvant chemotherapy in FIRST.

AstraZeneca reported performing a range of analyses to explore baseline characteristics in FALCON that could have influenced efficacy in the visceral disease subgroups; however, to date, no clear biological explanation has been found. Overall, disposition, demography and baseline characteristics of patients were considered well balanced between the fulvestrant and anastrozole treatment groups in FIRST and FALCON.[3]

FALCON

Of the 462 patients randomized in FALCON, 230 patients were randomized to the fulvestrant treatment group and 232 were allocated to the anastrozole group. The treatment groups were considered well balanced for baseline demographic and prognostic characteristics; however, there did appear to be a greater number of patients with visceral disease in the fulvestrant group (8% proportional difference) and aged ≥ 65 years (8% proportional difference). The median age of patients was 64 and 62 years in the fulvestrant and anastrozole groups, respectively. A greater proportion of patients were aged ≥ 65 years in the fulvestrant group (47%) compared with the anastrozole group (39%). Most patients were white (76%), had a WHO performance status of 0-1 (96%), receptor status ER+PgR+ (77%), metastatic disease (87%), and visceral disease (55%). All patients were human epidermal growth receptor status negative except for one patient in the anastrozole group.

Non-visceral Disease[3]

Among patients with non-visceral disease, the anastrozole group compared to the fulvestrant group had more patients with WHO performance status 0 than 1 and less patients with ER+PgR+ hormone status. Compared with the total population, there were more patients with locally advanced disease in the fulvestrant (27.4% vs. 12%) and anastrozole (28.3% vs. 14%) treatment groups with non-visceral disease only. Also compared with the total population, more patients had bone only disease in the fulvestrant (25.3% vs. 10%) and anastrozole (21.2% vs. 10%) treatment groups with non-visceral disease only.

FIRST

Of the 205 patients randomized in FIRST, 102 patients were randomized to the fulvestrant treatment group and 103 were allocated to the anastrozole group. The treatment groups were considered well balanced for baseline demographic and prognostic characteristics; however, there did appear to be a greater number of patients with visceral disease in the anastrozole group (9.2% proportional difference) and previous treatment with hormonal treatment in the fulvestrant group (5.2%), and no previous endocrine treatment in the

anastrozole group (6.1%). The median age of patients was 66 and 68 years in the fulvestrant and anastrozole groups, respectively. Most patients had a receptor status ER+PgR+ (76%), metastatic disease (82%), and visceral disease (52%). Human epidermal growth receptor status was negative for approximately 47% of patients in the FIRST study; however, 34% of patients' status was unknown.

Non-visceral Disease Only[3]

There were more patients with ER+PgR+ in the anastrozole group in the non-visceral disease subgroup compared with the total population (80% vs. 75.7%). Compared with the total population, there were more patients with locally advanced disease in the fulvestrant (35.2% vs. 18.6% and anastrozole (40% vs. 17.5%) treatment groups with non-visceral disease only.

Table 4: Baseline patient characteristics in the FALCON and FIRST trials

	Total Population				Non-visceral Disease[3]			
Trials	**FALCON**		**FIRST[3,31]**		**FALCON**		**FIRST**	
Treatment Groups	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole
No. patients randomized	230	232	102	103	95	113	54	45
Baseline patient characteristics, n (%) unless otherwise specified								
Median age, (range)	64.0 (38-87)	62.0 (36-90)	66 (40-89)	68 (48-87)	64.0 (43-86)	63.0 (36-89)	67 (40-89)	73 (52-87)
WHO performance status[α]								
0	117 (51)	115 (50)	53 (52.0)	57 (55.3)	58 (61.1)	64 (56.6)	27 (50.0)	27 (60.0)
1	106 (46)	105 (45)	42 (41.2)	41 (39.8)	33 (34.7)	43 (38.1)	24 (44.4)	16 (35.6)
2	7 (3)	12 (5)	7 (6.9)	5 (4.9)	4 (4.2)	6 (5.3)	3 (5.6)	2 (4.4)
Geographic region								
US/Canada	25 (11)[5]	24 (10)[5]	8 (7.85)	5 (4.85)	12 (12.6)	14 (12.4)	4 (7.4)	1 (2.2)
Non-US/Canada	205 (89)[5]	208 (90)[5]	94 (92.15)	98 (95.15)	83 (87.4)	99 (87.6)	50 (92.6)	44 (97.8)
Receptor Status								
ER+PgR+	175 (76)	179 (77)	78 (76.5)	78 (75.7)	73 (76.8)	83 (73.5)	41 (75.9)	36 (80.0)
ER+PgR-	44 (19)	43 (19)	19 (18.6)	19 (18.4)	16 (16.8)	26 (23.0)	12 (22.2)	6 (13.3)
ER+PgR unknown	10 (4)	7 (3)	1 (1.0)	3 (2.9)	6 (6.3)	2 (1.8)	0 (0.0)	2 (4.4)
ER-PgR+	1 (<1)	3 (1)	3 (2.9)	3 (2.9)	0 (0.0)	2 (1.8)	1 (1.9)	1 (2.2)
ER-PgR-	0	0	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disease stage								
Locally advanced	28 (12)	32 (14)	19 (18.6)	18 (17.5)	26 (27.4)	32 (28.3)	19 (35.2)	18 (40.0)
Metastatic	202 (88)	200 (86)	83 (81.4)	85 (82.5)	69 (72.6)	81 (71.7)	35 (64.8)	27 (60.0)
Site of disease								
Visceral disease	135 (59)	119 (51)	48 (47.1)	58 (56.3)	0 (0)	0 (0)	0 (0)	0 (0)
Bone or musculoskeletal only	24 (10)	24 (10)	10 (9.8)	8 (7.8)	24 (25.3)	24 (21.2)	10 (18.5)	8 (17.8)
Breast only	3 (1)	2 (1)	1 (1.0)	0	3 (3.2)	2 (1.8)	1 (1.9)	0 (0)
Skin or soft tissue only	8 (3)	6 (3)	1 (1.0)	0	8 (8.4)	6 (5.3)	1 (1.9)	0 (0)
Other non-visceral	60 (26)	81 (35)	NR	NR	NA	NA	NA	NA
Previous treatment								
Chemotherapy								
Locally advanced or metastatic breast cancer	36 (16)	43 (19)	0	0	16 (16.8)	15 (13.3)	0 (0.00)	0 (0.00)
Adjuvant	35 (15)	27 (12)	29 (28.4)	25 (24.3)	9 (9.5)	13 (11.5)	10 (18.52)	7 (15.56)
Neoadjuvant	11 (5)	16 (7)	NR	NR	6 (6.3)	10 (8.8)	NR	NR
Radiotherapy	53 (23)	50 (22)	36 (35.3)[3]	34 (33.0)[3]	17 (17.9)	25 (22.1)	15 (27.8)	16 (35.6)
Immunotherapy	NR	NR	0[3]	0[3]	NR	NR	NR	NR
Hormonal therapy	2 (1)	1 (<1)	29 (28.4)[3]	23 (22.3)[3]	1 (1.1)	1 (0.9)	14 (25.9)	8 (17.8)
Completed hormonal treatment >12 months prior to randomisation	1 (<1)	1 (<1)	28 (27.5)[3]	23 (22.3)	1 (1.1)	1 (0.9)	13 (24.1)	8 (17.8)
Prior endocrine treatment								
No prior endocrine treatment	NR	NR	73 (71.6)	80 (77.7)	NR	NR	NR	NR
Completed adjuvant endocrine treatment for early disease > 12 months prior to random assignment	NA	NR	28 (27.5)	23 (22.3)	NR	NR	NR	NR

Abbreviations: ER = estrogen receptor, **NA** = not applicable, **NR** = not reported, **PgR** = progesterone receptor
Notes: [α]For WHO performance status, 0 represents normal activity, 1 represents restricted activity, and 2 represents being in bed 50% of the time or less

c) Interventions

In both the FALCON and FIRST trials, patients allocated to the experimental treatment groups of each trial received fulvestrant at a dose of 500 mg on days 0, 14 (±3), 28 (±3), and every 28 (±3) days thereafter. Anastrozole was administered at a dose of 1 mg orally daily and dispensed on the same schedule as fulvestrant. Treatment was continued until they experienced disease progression or other events requiring discontinuation such as adverse events, protocol non-adherence, or patient's decision to withdraw. In FALCON, no fulvestrant dose reductions were permitted; in FIRST, dose reductions or modifications were not permitted or recommended.[3] In FALCON, patients with concomitant anticancer treatment except for bisphosphonates or denosumab were excluded; chronic concomitant bisphosphonate therapy for prevention of bone metastases was not permitted during the FIRST study.[31] Crossover was not reported in either trial.

In FALCON, the median duration of actual exposure to fulvestrant was 14.7 months (range 0.9-37.7) and to anastrozole was 13.9 months (range 0.2 to 36.0). In the visceral disease subgroup, the median duration of treatment exposure was 12.0 months and 14.3 months in the fulvestrant and anastrozole groups, respectively. In the non-visceral disease subgroup, median duration of treatment exposure was 19.4 months and 13.1 months in the fulvestrant and anastrozole groups, respectively. In FIRST, the median drug exposure was 9.2 months (range 1 to 20.5) in the fulvestrant group and 6.1 months (range 0 to 19.8) in the anastrozole group. Dose interruptions due to an AE were reported in 11 patients each in the fulvestrant (4.8%) and anastrozole (4.7%) in FALCON, respectively. In the visceral disease subgroup, the median duration of treatment exposure was 9.2 months and 5.6 months in the fulvestrant and anastrozole groups, respectively. In the non-visceral disease subgroup, median duration of treatment exposure was 9.2 months and 8.3 months in the fulvestrant and anastrozole groups, respectively.

d) Patient Disposition

The disposition of patients in the FALCON and FIRST trials is provided in Table 5.

FALCON
In FALCON, all randomized patients received allocated treatment except for two patients in the fulvestrant group due to patient decision. At the time of primary data-analysis of PFS, 73% and 79% of patients in the fulvestrant and anastrozole group discontinued study treatment, respectively. In both groups, worsening of condition which included disease progression was the primary reason for treatment discontinuation. Of those included in the intention-to-treat analysis, 93 (40%) and 101 (44%) patients terminated study. Reasons for termination of the study treatment in the fulvestrant and anastrozole group were: died (63 and 68 patients), patient decision (10 and 10), lost to follow-up (1 and 0), and eligibility criteria not fulfilled (2 and 3).

More patients in the fulvestrant group had at least one important protocol deviation compared with the anastrozole group (45.2% versus 33.6%).[11] The reason for this difference was reported to be driven by mis-stratification (20.0% versus 16.8% of patients) and RECIST timing issues (14.8% versus 9.5% of patients), respectively. Mis-stratification was driven by the prior chemotherapy for locally advanced or metastatic disease stratum: overall, 47 (10.2%) patients were assigned as having received prior chemotherapy of these, the majority (45) were actually recorded as having prior chemotherapy for early disease (neo-adjuvant and/or adjuvant) on the eCRF. A further 4 (0.9%) patients were assigned as having received no prior chemotherapy on the IVRS system, but reported as having received prior chemotherapy on the eCRF. Although more patients were mis-stratified in

the fulvestrant group than anastrozole, the incidence of discordance was similar in both treatment groups across all three stratification factors.

RECIST issues included baseline recist scan >28 days before randomization or after randomization and missing bone/RECIST scans. Missing RECIST data was reported to unlikely result in biased results and there was no evidence of bias due to different scanning frequency between groups. Other protocol deviations included blinding (1.5% of total population), inclusion/exclusion criteria (5.8%), prohibited medication (2.6%), safety issues (5.8%), treatment compliance (1.5%), and treatments and randomization (18.8%).

FIRST

In FIRST, all randomized patients received allocated treatment except for one patient in the fulvestrant group. At the time of primary data-analysis of CBR, 36% and 49% of patients in the fulvestrant and anastrozole group, respectively, discontinued study treatment. In both groups, disease progression was the primary reason for treatment discontinuation.

A total of 198 (97%) patients had no major protocol deviations at the time of the data cut-off.[31] Three patients in the fulvestrant group had a major protocol deviation: did not meet inclusion criteria, randomized but received no randomized treatment, and screening bone lesion confirmation not done. Four patients in the anastrozole group had a major protocol deviation: did not meet inclusion criteria, received prohibited concomitant medication, and screening abdominal assessment done after randomization. Overall, there were few major protocol deviations in the population and appeared to be balance between treatment groups

In the follow-up analysis, subsequent breast cancer treatment was recorded for 64 and 69 patients in the fulvestrant and anastrozole groups, respectively.[26] Similarly, 34 and 50 patients in the fulvestrant and anastrozole groups, respectively, received subsequent endocrine therapy.[26]

At the follow-up analysis for OS, 23 patients were alive and 63 had died in the fulvestrant group.[25] For anastrozole, at the follow-up analysis for OS, 10 patients were alive and 74 patients had died.[25] Sixteen and 19 patients in the fulvestrant and anastrozole groups, respectively, did not contribute additional data during the OS follow-up extension due to site or patient declining participation.[25] No patients participating in the OS phase were lost to follow-up and the survival status at data cut-off was known for all patients.[25]

Non-visceral Disease[3]

Overall patient disposition was similar between the total population and patients with non-visceral disease only in FALCON and FIRST. Of note, lower proportions of patients in both trials (non-visceral disease only versus total population) discontinued treatment due to the primary reason of worsening of condition/disease progression; correspondingly, more patients were receiving treatment at data-cutoff.

Table 5: Patient disposition in the FALCON and FIRST trials

	Total Population				Non-visceral Disease[3]			
Trials	**FALCON**		**FIRST[2]**		**FALCON**		**FIRST**	
Treatment Groups, n (%)	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole
Patients randomized	230	232	102	103	95	113	54	45
Received allocated treatment	228 (99)	232 (100)	101 (99)	103 (100)	95 (100)	113 (100)	54	45
Did not receive allocated treatment	2 (1)	0	1 (1)	0	0	0	NR	NR
Patients discontinued study treatment	167 (73)	183 (79)	37 (36)	50 (49)	0	0	NR	NR
Primary reasons for discontinuation:								
Worsening of condition/disease progression[*]	134 (58)	158 (68)	28 (27)	38 (37)	47 (49.5)	73 (64.6)	6 (12.5)	13 (22.4)
Adverse events	16 (7)	11 (5)	2 (2)	3 (3)	8 (8.4)	5 (4.4)	2 (4.2)	0 (0)
Patient decision/voluntary patient discontinuation	10 (4)	10 (4)	1 (1)	0	2 (2.1)	5 (4.4)	13 (27.1)	18 (31.0)
Non-adherence to protocol	3 (1)	1 (0.4)	NR	NR	1 (1.1)	1 (0.9)	NR	NR
Lost to follow-up	1 (0.4)	0	NR	NR	1 (1.1)	0	NR	NR
Other	3 (1)	3 (1)	5 (5)	8 (8)	2 (2.1)	3 (2.7)	5 (10.4)	4 (6.9)
Patients ongoing in study at data cut-off[&]	137 (60)	131 (56)	64 (63)	53 (51)	34 (35.8)	26 (23.0)	41 (85.4)	27 (46.6)
Protocol deviations								
Any deviation	14 (3)[%]		NR		NR	NR	NR	NR
Major deviation[3]	145 (63.04)	121 (52.15)	3 (2.94)	4 (3.88)	52	67	1	2

Abbreviations: NR = not reported
Notes:[*]In FIRST, patients who discontinued study treatment due to disease progression entered the follow-up stage as per study plan; [%]Related to eligibility criteria, three patients were reported to have received previous endocrine therapy; [&]At primary data cut-off

Post-study treatment was received by patients in the FALCON and FIRST trials.[3] Among patients with non-visceral disease in FALCON (n=208), more patients in the anastrozole group (38.9%) received any anti-cancer therapy than in the fulvestrant group (28.4%). The most common therapies in the fulvestrant group were anastrozole, capecitabine, exemestane, and letrozole. The most common therapies in the anastrozole group were capecitabine, cyclophosphamide, everolimus, exemestane, fulvestrant, and paclitaxel. Among patients who received subsequent breast cancer therapy in FIRST (n=61; 61.6%), more patients in the anastrozole group (64.4%) received subsequent therapy than in the fulvestrant group (59.3%). Similarly to FALCON, the most common therapies in the fulvestrant group were arimidex, aromasin, cyclophosphamide, femara, letrozole, and paclitaxel. The most common therapies in the anastrozole group were arimidex, aromasin, cyclophosphamide, faslodex, femara, and investigational drug.

6.3.3 Limitations/Sources of Bias

Refer to Table 3 for a summary of key quality-related features of the FALCON and FIRST trials.

The main limitation with respect to both FALCON and FIRST are that patients with non-visceral disease represented subgroups of the total population. Visceral disease involvement was a subgroup in both trials and subgroup hypotheses can be specified in advance (which in principle could control error rates), however, visceral involvement was not reported as a pre-planned subgroup. These subgroup analyses are likely to lack power to detect differences, so most significant results will be falsely positive. Information regarding subgroups should be used with caution in making conclusions about subgroup efficacy, corresponding p-values cannot be interpreted with rigour and validity. Subgroup analyses do not account for the fact that patients have multiple characteristics that can simultaneously affect the likelihood of treatment effect. Furthermore, no sample size calculations with respect to visceral disease involvement subgroups were conducted in FALCON and FIRST.

The Submitter provided feedback on the pCODR Initial Recommendation which stated “The non—visceral subgroup from the FALCON study was prespecified. For FALCON the visceral group was specified after the finalization of the protocol, and included in the Statistical Analysis Plan (SAP) which was finalized prior to database lock and unblinding.” According to the Clinical Study Report (CSR) for FALCON, pre-unblinding changes to the planned analyses as described in the Clinical Study Protocol (CSP) and/or original SAP included the inclusion of visceral disease (yes/no) for subgroup analysis of PFS and as a covariate used for the Cox regression sensitivity analysis of PFS.[4]

With respect to dates, in FALCON, patient enrollment was from 17 October 2012 to 11 July 2014 with a data cut-off date of 11 April 2016. Through the pCODR systematic review of the pCODR submission and publically available documents, the CSP Edition 1 was dated 28 June 2012 with the SAP dated 05 August 2016.[4] Of note, the latest CSP that is currently publically available is dated 14 January 2013 and did not include subgroup analysis for the covariate of visceral disease involvement. [3,32] The protocol amendment was reported to have been made at the time recruitment started;[5] however, there remains uncertainty on the timing of when visceral involvement was included in the CSP in relation to the data cut-off date as well as finalization of the SAP. Although the non-visceral subgroup was reported to be pre-specified according to the Submitter, it was not pre-specified at the trial onset and thus not included in the original CSP/SAP.

As previously stated and to re-iterate, there is no reporting regarding visceral involvement with respect to:

- a subgroup hypothesis specified a priori;
- sample size and power estimation (as significant results can represent false positive results);
- stratification to ensure balance of prognostic factors and effect modifiers between treatment groups (thus possible confounding which can be linked to undoing of randomization by subgrouping);
- and formal adjustment for multiple comparison testing to control error rates (multiple statistical tests on the whole group and again on subgroups as well as multiple subgroup analyses on multiple outcomes).

In FALCON subgroup analyses (including visceral involvement) were conducted for a total of seven covariates. The greater the number of subgroup analyses performed in one trial, the lower the statistical power to detect a true difference and the more likely to arrive at a seemingly significant (but false) finding due entirely to chance.[7,10] If a statistical significance test is performed for each type of subgroup analysis, the probability of obtaining at least one statistical significant result (at $\alpha = 0.05$) is $1-(1-\alpha)^{\kappa}$, where κ = total number of tests. [7] For $\kappa = 7$, representing seven subgroup analyses, this probability is 30%, even if there is no true difference in effect.

In most cases, subgroup analyses are exploratory in nature and only indicative of possible subgroup effects; they do not have the statistical strength to support credible conclusions on treatment effects.[6] Subgroup analyses are enhanced by: biological plausibility of the proposed differential effect, support for consistent and similar findings from a number of studies, a priori predicted subgroup effects, and use of statistically sound methods to compensate for or adjust the type I error rate.[6-10] According to the Clinical Guidance Panel, there is some support for consistent and similar findings for the use of fulvestrant in this setting within the non-visceral subgroup (i.e., from FIRST), however, the predicted subgroup effect was not reported a priori and statistical methods were not reported to adjust for the type I error rate. The biological plausibility of the proposed differential effect is also uncertain as a rationale was not identified. It was reported that a range of post-hoc analyses have been performed, including exploration of baseline characteristics that could have influenced efficacy, failed to identify a clear biological explanation for the finding in the visceral disease subgroup.[4] Furthermore, according to the EPAR report, under "Uncertainties and limitations about favourable effects", it was reported that the superiority of fulvestrant over anastrozole seemed to be lost in the subgroup of patients with ER+ breast cancer with visceral metastases and no satisfactory explanation has been identified.[5] As more credible conditions are met (i.e., biological plausibility of the proposed differential effect, support for consistent and similar findings from a number of studies, a priori predicted subgroup effects, and use of statistically sound methods to compensate for or adjust the type I error rate), this increase the confidence that there are real treatment differences with fulvestrant by visceral involvement; based on the FALCON trial, only some credible conditions have been met.
The overall trial results in FALCON and FIRST suggest that fulvestrant significantly extends PFS compared with anastrozole and fulvestrant is not inferior to anastrozole with respect to CBR; the magnitude and direction of these efficacy results are applicable to the non-visceral disease subgroups. Overall, results from the non-visceral disease patient subgroups are difficult to interpret and should be interpreted with caution; at most results are hypothesis generating.

Further limitations specific to individual trials are listed below.

FALCON

- The Submitter provided feedback on the pCODR Initial Recommendation which noted "A global interaction test was conducted and suggested there was no statistically significant effect modifiers of fulvestrant identified, specifically, treatment effects on progression-free survival were largely consistent across the prespecified patient subgroups (p=0.1061), with certain exceptions including patients with visceral disease". A global interaction test was completed with a Cox-proportional hazard model to assess whether the treatment effect was consistent across the covariates.[1] A post-hoc interaction test to assess for consistency of the treatment effects across the visceral and non-visceral subgroups was also done.[1] Treatment effects were reported to be largely consistent across the pre-specified patient subgroup (global interaction test p=0.1061) in demonstrating no significant differential treatment effect by each covariate. The post-hoc interaction test across visceral and non-visceral subgroups gave a significant p-value of 0.0092.[1] According to the Clinical Study Report for FALCON, if the global interaction test was significant then the covariate by treatment interaction would be assessed individually.[3] The global interaction test was not significant, however, a post-hoc interaction test was conducted for the covariate of visceral involvement. The Clinical Study Report noted "treatment effect may be investigated in groups as defined by these covariates to locate the source and nature of any interactions or if that would aid interpretation of the trial results."[4] As the global interaction was "only marginally greater than the 10% significance level, it is pertinent to closely examine the consistency of the observed treatment effect across all pre-defined subgroups".[4] A global interaction test was conducted and suggested there were no statistically significant effect modifiers of fulvestrant identified, this includes the non-visceral disease subgroup. Given the small sample size in this subgroup analysis, it is possible that the test for interaction wasn't powered to determine statistical difference. The rationale for the subgroup analysis of visceral disease involvement was not reported and authors reported it is unknown why there is an observed difference in benefit by visceral disease involvement.
- Visceral involvement was not a stratification factor at baseline; stratification factors included locally advanced/metastatic disease, prior chemotherapy, and measurable or non-measurable disease at baseline. As treatment groups were not stratified for visceral involvement, balance of baseline patient characteristics may not hold. Among non-visceral disease, a greater proportion of patients treated with fulvestrant compared with anastrozole had WHO performance status of 0, ER+PgR+ status, and bone or musculoskeletal only disease; these imbalances of prognostic factors and effect modifiers may have biased results in favour of fulvestrant.
- The very large number of major protocol deviations that occurred during the trial was concerning (45.2% in the fulvestrant group and 33.6% in the anastrozole group). Most frequent deviations included mis-stratification and RECIST timing issues. While sensitivity 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. Of note, EMA assessment reported that these deviations are considered unlikely to affect the robustness of the study.[11]
- Patients with prior endocrine therapy for breast cancer were excluded, thus generalizability to the Canadian setting, where patients are commonly treated with endocrine therapy in the neoadjuvant or adjuvant setting, is unknown.

- HRQoL data was presented in conference abstract format only and has not gone through the peer review process.
- AstraZeneca funded the trial and was involved in study design, reviewing and interpreting the data, and writing the manuscript; the extent to which this may have influenced the results and reporting of the trial is unknown.

FIRST

- The trial was an exploratory study. The trial was open-label and therefore, investigators and patients were not blinded to treatment assignment. Therefore, the trial is at a high-risk for a number of different biases that can affect the internal validity (e.g., patient selection for eligibility, performance bias due to knowledge of assigned treatment). Patients in the fulvestrant group may have been more likely to adhere to experimental therapy and investigators may have been more likely to discontinue treatment in the anastrozole group. The assessment of subjective measures such as reporting of adverse events are likely to be biased. Although survival is a hard endpoint and less prone to bias, other more subjective outcomes like disease progression may be biased by an unblended investigator. However, scans for all patients were collated and reviewed in a blinded manner by an independent radiologist working for a contract services organization.
- There were multiple data-driven amendment changes (three amendments for follow-up analyses) that compromised the statistical analysis plan of the trial and cast doubt on the integrity of the obtained results and the magnitude of the reported treatment effect estimates.
    - No adjustments were made for multiple comparison testing; authors noted given FIRST was a phase II trial that no formal adjustments were made for multiple testing. A global interaction test was not reported to be conducted.
    - The updated analysis of OS results was not planned in the original protocol but was added after TTP results were analyzed. Authors noted this subsequent protocol amendment was made to address whether the extension of disease control would translate into an improvement in OS. Overall, OS was assessed in several post-hoc analyses after multiple protocol amendments (related to percentage of OS maturity) and results should be interpreted with caution.
- Visceral involvement was not a stratification factor at baseline; stratified randomization was by center only. As treatment groups were not stratified for visceral involvement, balance of baseline patient characteristics may not hold. Among non-visceral disease, patients treated with fulvestrant compared with anastrozole were younger (median age of 67 versus 73 years), had locally advanced disease, and receive adjuvant treatment. However, a greater proportion of patients treated with anastrozole compared with fulvestrant had WHO performance status of 0, ER+PgR+ status, and received radiotherapy. These imbalances of prognostic factors and effect modifiers may have biased results, however, it is difficult to estimate in which direction the potential bias might influence results.
- The trial did not collect data on health-related QoL; thus the direction and degree to which fulvestrant affects patient-reported QoL parameters in post-menopausal women with advanced hormone receptor-positive breast cancer is unknown from the FIRST trial.
- No participating centres were located in Canada and thus generalizability to the Canadian setting is unknown.

- AstraZeneca funded the trial, however, limited information is known regarding the extent of the funder's role in the conduct of the trial (e.g., study design, treatment administration, data collection, database access. The extent to which this may have influenced the results and reporting of the trial is unknown.

6.3.3.1 Detailed Outcome Data and Summary of Outcomes

A summary of the key efficacy results from the FALCON and FIRST trial can be found in Table 6.

Table 6: Efficacy results in the FALCON and FIRST trials

Population	Total Population				Non-Visceral Disease[3]			
	FALCON		FIRST[25]		FALCON		FIRST	
	Fulvestrant (N=230)	Anastrozole (N=232)	Fulvestrant (N=102)	Anastrozole (N=103)	Fulvestrant (N=48)	Anastrozole (N=58)	Fulvestrant (N=54)	Anastrozole (N=45)
Median follow-up, months	25.0[23]		29.1[3]	32.8[3]	25.72	25.23	60.8	39.3
Patients remaining on treatment, n (%)	61 (27)	49 (21)	64 (62.7)	34 (35.8)	34 (35.8)	26 (23.0)	41 (85.4)	27 (46.6)
Primary Outcome (FALCON) - PFS[$]								
No. PFS events (%)	143 (62)	166 (72)	63 (61.8)[11]	79 (76.7)[11]	51 (53.7)	79 (69.9)	26 (48.1)	30 (66.7)
Median PFS, months (95%CI)	16.6 (13.83-20.99)	13.8 (11.99-16.59)	23.4[11]	13.1[11]	22.3 (16.6-32.8)	13.8 (11.0-16.6)	34.0 (24.1-44.4)	21.3 (13.1-31.6)
HR (95%CI, two-sided p value)	0.797 (0.637-0.999, p=0.0486)		0.66 (0.47-0.92, p=0.01)[11]		0.592 (0.419-0.837; p = 0.0030)		0.58 (0.34-0.99; p = 0.05)	
Primary Outcome (FIRST) - CBR								
No. (%) patients achieving CB	180 (78)	172 (74)	74 (72.5)[11]	69 (67.0)[11]	83 (87.4)	85 (75.2)	46 (85.2)	30 (66.7)
OR(95%CI, p-value)	1.25 (0.82-1.93, p=0.3045)		1.30 (0.72-2.38, p=0.386)		2.242 (1.087-4.866; p = 0.0285)		2.875 (1.110-7.933; p = 0.029)	
ORR								
No. (%) patients achieving ORR[^]	89 (46)[2$]	88 (45)[$2]	89 (36.0)[2]	93 (35.5)[2]	35 (50.0)	38 (43.2)	15 (34.1)	14 (37.8)
OR (95%CI, p-value)	1.07 (0.72-1.61, p=0.7290)		1.02 (0.56-1.87, p=0.947)		1.380 (0.724-2.646; p = 0.3276)		0.850 (0.340-2.124; p = 0.726)	
DoR, median months (95%CI)	20.0 (15.90-27.63)	13.2 (10.64-16.72)	Not reached	14.2[2]	24.8 (19.6-Not reached)	16.7 (10.9-24.7)	Not reached	11.1 (7.4-11.1)
Overall Survival[%]								
Median OS, months	Not calculated[%]		54.1	48.4	Not calculated		76.6	60.9
No. (%) patients died	67 (29)	75 (32)[25]	63 (61.8)	74 (71.8)	18 (18.9)	33 (29.2)	29 (53.7)	26 (57.8)
HR (95%CI, p-value)	0.88 (0.63-1.22, p=0.4277)		0.70 (0.50-0.98, p=0.04)		0.601 (0.347-1.042; p = 0.0696)		0.68 (0.40-1.18; p = 0.171)	
HrQoL[4]								
Improved[ß] TOI and total FACT-B scores from baseline to Week 144, %	26.4-45.0 and 20.0-35.8	18.6-32.9 and 22.7-37.9	NA	NA	NR	NR	NA	NA
Time to deterioration for TOI and FACT-B, HR (95%CI, p-value)	0.90 (0.70-1.15, p=0.4008) 0.94 (0.66-1.07, p=0.1594)		NA	NA	NR	NR	NA	NA

wsAbbreviations: AE = adverse event, **CB =** clinical benefit, **CBR** = clinical benefit rate, **CI =** confidence interval, **DoR** = duration of response, **FACT-B** = Functional Assessment of Cancer Therapy for Breast Cancer, **HR =** hazard ratio, **HrQoL =** health-related quality of life, **NA** = not applicable, **NR** = not reported, **OR** = odds ratio, **ORR** = objective response rate, **OS** = overall survival, **PFS =** progression-free survival, **SD** = standard deviation, **TOI =** Trial Outcome Index

Notes: *HR < 1 favours fulvestrant; ^Among patients with measurable disease at baseline/evaluable patients; [%]Due to insufficient follow-up time (31% maturity); [ß]TOI (≥ +6 points) and FACT-B (≥ +8 points); [$]Denominators for these calculations were 193 for fulvestrant and 196 for anastrozole; [4]Time to disease progression (equivalent to PFS), 75% progression follow-up analysis

Efficacy Outcomes

Overall Survival (OS)

FALCON
At the time of data analysis, 67 (29%) and 75 (32%) patients died in the fulvestrant and anastrozole groups, respectively. Median OS could not be calculated because of insufficient follow-up time which represented 31% maturity at a median follow-up of 25.0 months.[23]

Non-visceral Disease[3]
At the time of data analysis, 18 (18.9%) and 33 (29.2%) patients died in the fulvestrant and anastrozole groups, respectively. Similar to the total population, the median OS could not be calculated for the visceral disease subgroups.

FIRST[25]
The protocol was amended to assess OS by unadjusted log-rank test after approximately 65% of all patients had died. At data cut-off, 61.8% and 71.8% of patients in the fulvestrant and anastrozole group had died, respectively. The median OS was 54.1 months and 48.4 months in the fulvestrant and anastrozole groups, respectively. At 3 years, 64% and 58% of patients in the fulvestrant and anastrozole groups, respectively, were event free; at five years, the equivalent values were 47% and 38%.

Treatment effect on OS was not statistically significant among all subgroup analyses. The OS benefit associated with fulvestrant (confidence intervals excluded the value of 1) was only evident among: all patients, patients with no prior chemotherapy, patients with measurable disease, and patients with no prior endocrine therapy. With respect to subgroups of interest, OS was not statistically improved with fulvestrant compared with anastrozole for both ER+/PgR+ (no and yes) and visceral involvement (no and yes). There was no reporting for the subgroup of locally advanced or metastatic disease.

Non-visceral Disease[3]
The median OS was 76.6 months and 60.9 months in the fulvestrant and anastrozole groups, respectively. OS was not statistically improved with fulvestrant among patients with non-visceral compared with visceral disease.

Progression-free Survival (PFS) – Primary Outcome of FALCON

FALCON

There were 309 progression events (target of 306 events) at data cut-off with 143 in the fulvestrant group and 166 in the anastrozole group. Fulvestrant was associated with a statistically significant improvement in PFS compared with anastrozole with median PFS of 16.6 versus 13.8 months, a difference in medians of 2.8 months (HR=0.797, 95%CI: 0.637-0.999).

Treatment effect on PFS was consistent across pre-specified patient subgroups with the following exceptions: patients with visceral disease, patients with previous chemotherapy for locally advanced or metastatic disease, patients with non-measurable disease, and patients who were not estrogen receptor-positive and progesterone receptor-positive at baseline. With respect to subgroups of interest, PFS was statistically improved with fulvestrant compared with anastrozole for metastatic disease, ER+/PgR+ at baseline, and

non-visceral disease as seen in Table 7. The PFS benefit associated with fulvestrant (confidence intervals included the value of 1) was not evident among subgroups of patients with locally advanced disease, no ER+/PgR+ at baseline, and visceral disease. Authors highlighted that for the large subgroup of patients with visceral disease (135 and 119 patients in the fulvestrant and anastrozole groups, respectively), there was no statistical significant difference in PFS with fulvestrant compared with anastrozole (HR=0.99, 95%CI: 0.74-1.33).[5]

Non-visceral Disease[3]

The median PFS among patients with non-visceral disease was 22.3 versus 13.8 months in the fulvestrant and anastrozole groups, respectively; this reflects a difference in medians of 8.5 months which was greater than that seen in the total population by treatment.

Table 7: Subgroup data for PFS for FALCON[5]

	Fulvestrant (N=230)	Anastrozole (N=232)	
Subgroup	**n/N (%)**	**n/N (%)**	**PFS HR (95%CI)**
Breast cancer type			
Locally advanced	11/28 (39.3)	14/32 (43.8)	0.79 (0.36-1.73)
Metastatic	132/202 (65.3)	152/200 (76.0)	0.78 (0.62-0.99)
Prior chemotherapy			
Yes	31/36 (86.1)	33/43 (76.7)	1.08 (0.66-1.77)
No	112/194 (57.7)	133/189 (70.4)	0.75 (0.59-0.97)
Measurable disease			
Yes	124/193 (64.2)	143/196) (73.0)	0.76 (0.60-0.97)
No	19/37 (51.4)	23/36 (63.9)	0.99 (0.53-1.82)
ER+/PgR+			
Yes	103/175 (64.2)	127/179 (70.9)	0.73 (0.56-0.94)
No	40/55 (72.7)	39/53 (73.6)	1.04 (0.67-1.62)
Visceral disease			
Yes	92/135 (68.1)	87/119 (73.1)	0.99 (0.74-1.33)
No	51/95 (53.7)	79/113 (69.9)	0.59 (0.42-0.84)

Abbreviations: ER = estrogen receptor, **HR** = hazard ratio, **PgR** = progesterone receptor, **PFS** = progression-free survival
Notes: *HR < 1 favours fulvestrant

FIRST

Median PFS was not reported in the FIRST study publication. At data cut-off, 29.4% and 41.7% of patients treated with fulvestrant and anastrozole had progressed. At the primary analysis, time to progression (TTP) was significantly longer with fulvestrant (median TTP not reached) and was 12.5 months for anastrozole (HR=0.63, 95%CI: 0.39-1.00, p=0.0496). At the follow-up analysis of OS, median TTP was 23.4 months and 13.1 months in the fulvestrant and anastrozole groups, respectively; this corresponded to a 34% reduction in risk of progression.[25,26]

With respect to subgroups of interest, TTP was consistent across all pre-specified subgroups, however, was only statistically significant among all patients, patients <65 years, patients with no prior chemotherapy, and patients with measurable disease.[26]

Non-visceral Disease[3]

After a request for additional data, median PFS was reported to be 34.0 months and 21.3 months in the fulvestrant and anastrozole groups, respectively; this corresponds to a difference in medians of 12.7 months. There was a statistically significant difference in PFS with fulvestrant compared with anastrozole (HR=0.58, 95%CI: 0.34-0.99, p=0.05).

Objective Response Rate (ORR)

FALCON
Among patients with measurable disease, the ORR was 46% and 45% in the fulvestrant and anastrozole group; the difference in ORR was not statistically significant.

Non-visceral Disease[3]
The ORR among patients with non-visceral disease was 50.0% and 43.2% in the fulvestrant and anastrozole group, both ORRs were greater in the non-visceral disease compared with the total population.

FIRST
Among evaluable patients, fulvestrant and anastrozole had almost identical ORR with 36.0% and 35.5%, respectively.

Non-visceral Disease[3]
The ORR among patients with non-visceral disease was 34.1% and 37.8% in the fulvestrant and anastrozole group, both ORRs were greater in the non-visceral disease compared with the total population.

Duration of Response (DoR)

FALCON
Among patients with measurable disease at baseline, the median DoR was longer in the fulvestrant group with 20.0 months than in the anastrozole group with 13.2 months. The expected duration of response (EDoR) was 11.4 and 7.5 months in the fulvestrant and anastrozole groups, respectively (EDoR ratio=1.52, 95%CI: 1.03-2.26, p=0.0367).

Non-visceral Disease[3]
The median DoR was greater in both treatment groups in the non-visceral disease with 24.8 months and 16.7 months in the fulvestrant and anastrozole groups, respectively. The upper 95%CI of the DoR in the fulvestrant group was not reached.

FIRST
The median DoR for fulvestrant had not been reached at the time of the analysis and was 14.2 months for anastrozole.

Non-visceral Disease[3]
The median DoR was [redacted] in the fulvestrant group and was [redacted] months in the anastrozole group in the non-visceral disease subpopulation.(*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed, whichever is earlier*)

Clinical Benefit Rate (CBR) – Primary Outcome of FIRST

FALCON
CBR was not statistically significantly different between treatment groups with CBRs of 78% and 74% in the fulvestrant and anastrozole groups, respectively. The median duration

of clinical benefit was 22.1 months with fulvestrant and 19.1 months with anastrozole. The expected duration of clinical benefit (EDoCB) was 21.9 months with fulvestrant and 17.5 months with anastrozole (EDoCB ratio=1.26, 95%CI: 0.99-1.59, p=0.0561).

Non-visceral Disease[3]

Similar to the total population, CBR was not statistically significantly difference between treatment groups of non-visceral disease with CBRs of 83% and 85% in the fulvestrant and anastrozole groups, respectively.

FIRST

The analysis of the primary endpoint of CBR demonstrated that fulvestrant was at least as effective as anastrozole with CBR of 72.5% and 67.0%, respectively. The absolute treatment difference was 5.6% (95%CI: -7.8-15.8). The blinded, independent review of the RECIST data that was used to determine CBR resulted in concordance rates of 88.4% and 86.3% for fulvestrant and anastrozole, respectively. Complete response was observed in no patients in the fulvestrant group and 1 (1%) patient in the anastrozole group. Partial response (31.4% and 31.1%) and stable disease ≥24 weeks (41.2% and 35.0%) was observed in the fulvestrant and anastrozole groups, respectively. No clinical benefit was observed in 28 (27.5%) and 34 (33.0%) patients in the fulvestrant and anastrozole groups, respectively. The duration of clinical benefit was not reached for both treatment groups at the time of analysis.

Non-visceral Disease[3]

CBRs among patients with non-visceral disease were [redacted] than patients in the overall total population in the fulvestrant ([redacted] vs. [redacted]) and anastrozole ([redacted] vs. [redacted]) treatment groups. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed, whichever is earlier*)

Quality of Life (HrQoL)

FALCON

HrQoL was assessed in the FALCON study using the Trial Outcome Index (TOI) derived from the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) questionnaire and FACT-B total score. Changes from baseline in FACT-B total score of ≥+8 points were classified as improved, ≤-8 points as deteriorated, and between -8 and +8 points as stable. Changes from baseline in TOI of ≥+6 points were classified as improved, ≤-6 as deteriorated, and between -6 and +6 points as stable.[4] Overall compliance to FACT-B was 91.3% with fulvestrant (range 66.7-94.3%) and 92.2% with anastrozole (range 60.0-97.4%).[4] Compliance to FACT-B during treatment ranged from 84.6% to 100%.[4] Overall, mean FACT-B and Trial Outcome Index scores were reported to be maintained and similar in both treatment groups. The mean change from baseline in TOI (scale range 0-92) and FACT-B total score (scale range 0-144) remained stable (approximately ±3 points to Week 132), similar results were maintained in the FACT-B subscales.[4] There was no clinically meaningful difference in the proportion of patients who had improved FACT-B total score and TOI with fulvestrant compared with anastrozole.[4] Approximately one-third of patients had improved TOI (≥ +6 points) and FACT-B (≥ +8 points) total scores from baseline up to Week 144 with fulvestrant treatment (ranges of 26.4%-45.0% and 20.0-35.8%, respectively) and anastrozole treatment (ranges 18.6%-32.9% and 22.7%-37.9%, respectively).[4] The time to deterioration did not differ significantly between treatment groups for Trial Outcome

Index Score (HR=0.90, 95%CI: 0.70-1.15, p=0.4008) and FACT-B total score (HR=0.84, 95%CI: 0.66-1.07, p=0.1594).[4]

FIRST

The FIRST study did not assess HrQoL.

Harms Outcomes

The FALCON and FIRST trials provided data on the harm outcomes of interest. Harms data are summarized in Table 8. A post-hoc analysis of safety in the visceral disease subgroups in FALCON and FIRST was also conducted and results are presented in Table 9.No statistical comparisons of the rates of adverse events (AEs) between trial arms were reported in FALCON; two-sided Fisher's exact test was used to assess significant differences between treatment arms in ten pre-specified AEs in FIRST. All patients who received at least one dose of study treatment were included in analyses of safety.

Adverse Events (AEs)

FALCON
AEs occurred in 116 (73%) and 173 (75%) patients in the fulvestrant and anastrozole groups, respectively. The number of patients who experienced grade 3 or higher AEs was 51 (22%) and 41 (18%) of patients in the fulvestrant and anastrozole groups, respectively. The most frequent AEs (≥10% of patients) reported in the fulvestrant group were: arthralgia (17%), hot flush (11%), fatigue (11%), and nausea (11%). The most frequent AEs (≥10% of patients) reported in the anastrozole group were: arthralgia (10%), hot flush (10%), and nausea (10%).

FIRST
A total of 143 (70.1%) patients experienced at least one AE. The most common AEs in the fulvestrant group were reported to be bone pain (13.9%), nausea (10.9%), arthralgia (9.9%), constipation (9.9%), vomiting (8.9%), and dyspnea (8.9%). The most common AEs in the anastrozole group were reported to be hot flashes (13.6%), headache (12.6%), bone pain (9.7%), arthralgia (8.7%), and myalgia (8.7%). There were no significant differences between treatments in the incidence of any of 10 pre-specified AEs; the pre-specified AEs were: endometrial dysplasia, GI disturbances, hot flashes, ischemic cardiovascular disorders, joint disorders, osteoporosis, thromboembolic events, urinary tract infections, vaginitis, and weight gain.

Serious Adverse Events (SAEs)

FALCON
SAEs occurred in 30 (13%) and 31 (13%) of patients in the fulvestrant and anastrozole groups, respectively. Causally related SAEs were experienced by 4 (1.8%) and 3 (1.3%) of patients in the fulvestrant and anastrozole groups, respectively.[1] SAEs considered causally related to the treatment occurred at a frequency of 0.4% (one patient) in the fulvestrant group and included: gastroenteritis; drug hypersensitivity, atrial fibrillation, and pulmonary embolism. SAEs considered causally related to the treatment occurred at a frequency of 0.4% (one patient) in the anastrozole group and included: pyelonephritis, deep vein thrombosis, or bile duct stone.

FIRST
At the primary analysis, the incidence of SAEs was 11.9% and 9.7% of patients in the fulvestrant and anastrozole groups, respectively. With respect to treatment-related AEs, in the fulvestrant group, the most common treatment-related AEs were hot flashes (7.9%), injection-site pain (5.0%), and hyperhidrosis (4.0%); in the anastrozole group, the most common treatment-related AEs were hot flashes (12.6%), arthralgia (5.8%), and headache (5.8%).

At the follow-up analysis of OS, 24 (23.8%) and 22 (21.4%) patients in the fulvestrant and anastrozole groups, respectively, experienced any SAE.[25] Any SAE related to death occurred in 3 (3.0%) and 5 (4.9%) patients in the fulvestrant and anastrozole groups, respectively.[25] Two SAEs were considered treatment-related, one case of hypertension and one case of pulmonary embolism, both in the fulvestrant treatment group.[25]

Withdrawals Due to Adverse Events (WDAEs)

FALCON
Any AE leading to discontinuation occurred in 16 (7%) and 11 (4.7%) patients in the fulvestrant and anastrozole groups, respectively. Among patients treated with fulvestrant, AEs leading to discontinuations included: peritonitis; neoplasms benign, malignant, and unspecified; drug hypersensitivity; hypersensitivity; brain oedema; cerebrovascular accident; dementia; haemorrhagic stroke; angina pectoris; atrial fibrillation; hypertensive crisis; chronic obstructive pulmonary disease; pulmonary embolism; abdominal pain; large intestine perforation; injection-site hypersensitivity; ALT increased; and AST increased. Among patients treated with anastrozole, AEs leading to discontinuations included: colon cancer; acute myocardial infarction; angina unstable; cardiac arrest; cardiac failure acute; cardio-respiratory arrest; deep vein thrombosis; jaundice cholestatic; and joint stiffness.

FIRST
Three patients in each treatment group discontinued treatment because of an AE.

Adverse Events of Interest

Local injection reactions (e.g., pruritus, urticaria)
In FALCON, injection-site hypersensitivity lead to discontinuation in one patient (0.4%) in the fulvestrant group. In FIRST, six patients (5.9%) reported 14 instances of injection-site pain.

Hematoma
One patient in the FALCON anastrozole treatment group and two patients in the FIRST fulvestrant treatment group had hematoma.[3]

Hepatic failure
No information was available on hepatic failure in FALCON or FIRST.

Table 8: Safety results in the FALCON and FIRST trials

	FALCON		FIRST	
	Fulvestrant (N=230)	**Anastrozole (N=232)**	**Fulvestrant (N=102)**	**Anastrozole (N=103)**
No. of patients in safety analysis	228	232	101	103
Median duration of exposure, months (range)	14.7 (0.9-37.7)	13.9 (0.2-36.0)	9.2 (1-20.5)	6.1 (0-19.8)
Adverse events, n (%)	116 (73)	173 (75)	143 (70.1)	
Grade ≥3 adverse events, n (%)	51 (22)	41 (18)	18 (17.8)[11]	11 (10.7)[11]
Serious adverse events, n (%)	30 (13)	31 (13.4)	12 (11.9)[11]	10 (9.7)[11]
Discontinued because of adverse events	16 (7)	11 (5)	3 (3.0)	3 (2.9)
Death due to adverse event^, n (%)	6 (2.6)	7 (3)	0 (0.0)	1 (1.0)
Adverse events of interest				
Local injection reactions				
Injection Site Eczema	1 (0.4)	0	0 (0.0)	1 (1.0)
Injection Site Urticaria	1 (0.4)	0	NR	NR
Injection Site Pain	11 (4.8)[11]	8 (3.4)[11]	6 (5.9)	0
Injection Site Pruritus	1 (0.4)	3 (1.3)	2 (2.0)	0
Hematoma[3]	0	1 (0.4)	2 (2.0)	0
Hepatic failure	NR	NR	NR	NR

Abbreviations: AE = adverse event, **NR** = not reported
Notes: ^No deaths because of adverse events were considered causally related to treatment/treatment-related

Table 9. Safety results in non-visceral and visceral disease subgroups in FALCON and FIRST

Trials	FALCON				FIRST			
	Visceral		Non-Visceral		Visceral		Non-Visceral	
Treatment Groups	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole
No. of patients in safety analysis	133	119	95	113	47	58	54	45
Adverse events, n (%)	90 (67.7)	93 (78.2)	76 (80.0)	80 (70.8)	34 (72.3)	44 (75.9)	37 (68.5)	28 (62.2)
Grade ≥3 adverse events, n (%)	29 (21.8)	16 (13.4)	22 (23.3)	25 (22.1)	8 (17.0)	6 (10.3)	10 (18.5)	5 (11.1)
Serious adverse events, n (%)	19 (14.3)	12 (10.1)	11 (11.6)	19 (16.8)	5 (10.6)	6 (10.3)	7 (13.0)	4 (8.9)
Discontinued because of adverse events	8 (6.0)	6 (5.0)	8 (8.4)	5 (4.4)	1 (2.1)	3 (5.2)	2 (3.7)	0
Death due to adverse event, n (%)	4 (3.0)	1 (0.8)	2 (2.1)	6 (5.3)	0	1 (1.7)	0	0
Adverse events of interest[3]								
Local injection reactions	1 (0.8)	0 (0)	2 (2.1)	0 (0)	NR	NR	NR	NR
Injection Site Eczema	1 (0.8)	0 (0)	NR	NR	0 (0)	1 (1.7)	NR	NR
Injection Site Urticaria	1 (0.8)	0 (0)	NR	NR	NR	NR	NR	NR
Injection Site Pain	6 (4.5)	3 (2.5)	5 (5.3)	7 (6.2)	4 (8.5)	0 (0)	2 (3.7)	0 (0)
Injection Site Pruritus	1 (0.8)	1 (0.8)	0 (0)	2 (1.8)	1 (2.1)	0 (0)	1 (1.9)	0 (0)
Hematoma	NR	NR	0 (0)	1 (0.9)	1 (2.1)	0 (0)	1 (1.9)	0 (0)
Hepatic failure	NR	NR	NR	NR	NR	NR	NR	NR
Abbreviations: NR = not reported								

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

The following supplemental issue was identified as relevant to the pCODR review of fulvestrant for hormonal treatment of non-visceral locally advanced or metastatic HER2- breast cancer in postmenopausal women, regardless of age, who have not been previously treated with endocrine therapy:

- Critical appraisal of the manufacturer-submitted network meta-analysis (NMA) comparing fulvestrant to palbociclib plus letrozole in the non-visceral population.

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 of Fulvestrant Compared with Palbociclib Plus Letrozole in the Non-Visceral Subgroup Only

7.1.1 Objective

The objective of this section is to summarize and critically appraise the methods and findings of the manufacturer-submitted NMA of fulvestrant with palbociclib plus letrozole for the non-visceral subgroup.

This critical appraisal was necessary as according to the PAG input, palbociclib is not yet funded in any province and PAG is seeking whether there is information comparing palbociclib plus letrozole to fulvestrant.

AstraZeneca does not believe this comparison would be appropriate as clinical experts have indicated that palbociclib plus letrozole is not the key comparator in the non-visceral subgroup for the following reasons:

- Palbociclib plus letrozole compared with letrozole alone was associated with improved PFS but not OS as well as greater toxicity. From the 2016 ASCO and NCCN 2017 guidelines, without compelling survival data or major differences in clinical benefit, clinicians and patients can exercise discretion in choice of whether or not to expose patients to the toxicity and treatment burden of palbociclib plus letrozole. Furthermore, endocrine therapy was called out as the therapy for consideration in patients with non-visceral disease, especially patients with clinical characteristics that predict for a hormone-receptor positive tumour.
- Public funding is not currently available as a first-line option. Palbociclib is under active negotiations and it is assumed it will eventually receive public funding. However, clinical expert opinion suggest that it would not the standard of care in patients with non-visceral disease, rather an option for patients that are fit, with visceral disease that wish to achieve efficacy, rather than maintain quality of life, and are willing to adhere to a complex treatment regimen.
- Palbociclib plus letrozole is likely to be reserved for the second-line rather than first-line setting, especially given its toxicity profile.

The pCODR Methods Team and CGP considered that palbociclib plus letrozole is a relevant comparator for patients with non-visceral as well as visceral disease. Palbociclib plus letrozole is under negotiations and will eventually receive public funding; furthermore, palbociclib plus letrozole would be used in the first-line setting dependent on resources as well as patient and clinician choice. The CGP noted that the use of palbociclib plus letrozole would not be reserved based on line of therapy (first- or second-line) but rather patient age and performance status.

7.1.2 Findings

The manufacturer submitted a NMA with the objective of comparing fulvestrant to palbociclib plus letrozole in the non-visceral disease population in the absence of a head to head trial.

A previously full NMA for the HTA submission in the European Union was sourced for trials reporting results for the non-visceral disease subgroup and to complete an indirect comparison within this subgroup. A systematic review was conducted for the full NMA. There were two objectives to the previous systematic review:

- To assess the clinical efficacy, safety, and tolerability associated with pharmacological interventions as first-line treatment for post-menopausal women with hormone receptor-positive, locally advanced or metastatic breast cancer who had no prior hormonal treatment; and
- To conduct a feasibility assessment for network meta-analysis to assess the comparative efficacy and safety of fulvestrant and relevant comparators.

Systematic Review Methodology of Full NMA
The trial protocol for the full NMA is presented in Table 1.

Table 1: Summary of trial protocol for systematic review for NMA

Item	Description	
Population	• Age: Adults (≥18 years) • Gender: Female patients (in particular post-menopausal) • Race: Any • Disease: HR+, HER2 negative locally advanced or metastatic breast cancer	
Intervention/	• Fulvestrant • Anastrozole • Letrozole • Tamoxifen • Toremifene • Exemestane • Abiraterone acetate • Megestrol acetate • Atamestane • Z-endoxifen • Palbociclib • Ribociclib	• Lapatinib • Everolimus • Bevacizumab • Docetaxel • Paclitaxel • Abemaciclib • Temsirolimus • Entinostat • Alpelisib • Taselisib • Pictilisib • Buparlisib
Comparators	• Any included intervention • Any pharmacological intervention • Placebo/best supportive care/observation	
Study design	RCTs	

Multiple databases (EMBASE, MEDLINE, MEDLINE In-Process, and Cochrane Central Register of Controlled Trials) were searched from database inception to 10 March 2016. Conference proceedings were hand searched for the last three years (2013 to 2015) in ASCO, ESMO, and the San Antonio Breast Cancer symposium. Additional steps (e.g., bibliography of systematic reviews and meta-analyses, references of included studies) to identify key studies were made.

Two independent reviewers conducted abstract review, full-text, and data extraction; any discrepancies between the two independent reviewers were reconciled by a third independent reviewer. The included RCTs were critically appraised using a tool based on the National Institute for Health and Care Excellence checklist as well as by means of a grade and Jadad score.

A flow diagram was presented for inclusion and exclusion of studies [not presented here]. Overall, 44 studies from 91 publications were reviewed; a total of 22 were considered for the qualitative part of the report and 11 contributed to the mixed treatment comparisons.

Included Studies for Non-Visceral Disease

The previous systematic review was conducted across a broad range of comparators and identified 22 studies for inclusion. The NMA report for non-visceral disease included a table summarizing patient characteristics of the trials of interest, trials which either included fulvestrant or palbociclib plus letrozole. Four trials were included: FALCON, FIRST, PALOMA-1, and PALOMA-2 (Table 2).

Fulvestrant is under review for non-visceral locally advanced or metastatic HER2- breast cancer in postmenopausal women who have not been previously treated with endocrine therapy. Across all four trials, almost all patients were HER2- and all patients were post-menopausal. Of note, non-visceral disease ranged from 41 to 56% and endocrine naïve ranged from 43 to 100% of patients in treatment arms within the included trials.

The manufacturer applied a 65% criteria to each of the characteristics, where the patient population should contain at least 65% of these relevant patients across each category. In this respect, PALOMA-2 was not further included as the analysis had only 44% and 43% of the treatment groups containing endocrine naïve patients. They also noted that the PALOMA-2 did not have non-visceral disease results for OS and the PFS results were not as impressive as seen in PALOMA-1. The manufacturer noted that this exclusion avoids potential bias in the analysis.

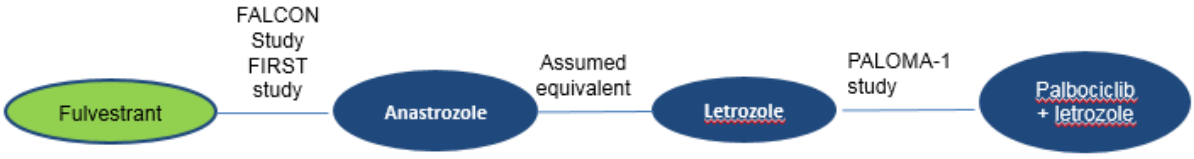
Table 2: Trials of interest[27]

Study name	Study included in the NMA for	Treatments	ITT N	Post-meno pause only?	Receptor status (%)				Endocrine naïve (%)	Prior chemotherapy (%)	Visceral disease (%)	Non-visceral disease (%)	NVD Results presented	
					HR +	ER +	Pg R+	HER 2-					OS	PFS
FALCON	Whole study population	FUL	230	YES	100	100	77	100	99	34	59	41	Yes	Yes
		ANA	232			99	78	99.6	100	35	51	49		
FIRST	Whole study population	FUL	102	YES	100	96	80	47	72	28	47	53	Yes	Yes
		ANA	103			97	79	48	78	24	56	44		
PALOMA-1	Subgroup of endocrine naïve population	PAL + LET	84	YES	100	100	NR	100	68	40	44	56	Yes	Yes
		LET	81						65	46	53	47		
PALOMA-2	Subgroup of endocrine naïve population	PAL + LET	444	YES	100	100	NR	100	44	48	48	52	No	Yes
		LET	222						43		50	50		

Network Meta-Analysis Methodology for Non-Visceral Disease

In order to conduct the indirect comparison, a decision was made to assume equivalence of anastrozole to letrozole (Figure 1).

Figure 1: Network diagram for comparison of fulvestrant to palbociclib plus letrozole[27]



Source: Manufacturer submission[27]

Hazard ratios and confidence intervals were available for all studies. Kaplain-Meier OS and PFS curves were also available for FIRST and FALCON and it was possible to test for proportional hazards which was met. Kaplan-Meier data were not available for PALOMA-1, therefore, it was not possible to test for proportional hazards; a decision was made to run the analysis on the limited information available for palbociclib plus letrozole and assume proportional hazards in the non-visceral disease group in PALOMA-1. A NMA based on the pooled hazard ratios was undertaken and the hazard ratios used in the indirect treatment comparison can be found in Table 3.

Table 3: Outcomes used from the included studies[27]

Study	Treatment (n)	Comparator (n)	OS hazard ratio (95% CI)	PFS hazard ratio (95% CI)
FALCON	Anastrozole (113)	Fulvestrant (95)	0.60 (0.35, 1.04)	0.59 (0.42, 0.84)
FIRST	Anastrozole (45)	Fulvestrant (54)	0.68 (0.40, 1.18)	0.58 (0.34, 0.99)
PALOMA 1	Letrozole (38)	Palbociclib + Letrozole (46)	Bone 0.50 (0.17, 1.47) Other (non visceral) 1.02 (0.53, 1.94) Combined[1] 0.80 (0.46, 1.40)	Bone 0.29 (0.09, 0.95) Other (non visceral) 0.40 (0.20, 0.81) Combined[2] 0.36 (0.20, 0.66)

[1] http://www.burtonsys.com/climate/composite_standard_deviations.html
[2] Calculated by combining the 'bone' and 'other (non-visceral') subgroups for the purposes of this study

The following assumptions were reported to be required to complete the NMA for the subgroup:

- **AIs have similar efficacy:** most guidelines recommend AIs as options without specifically suggesting one AI over another and AIs are considered standard of care. Furthermore, clinical opinion suggests AIs are considered interchangeable in terms of efficacy and safety.
- **Definition of non-visceral in PALOMA-1:** given the non-visceral patients in PALOMA-1 were reported to have either bone or other metastases, these two groups were combined.
- **Assumption of proportional hazards:** Kaplan-Meier data were not available in PALOMA-1 and it was not possible to test proportional hazards. It was assumed proportional hazards in the non-visceral group in PALOMA-1.

Bayesian ITC was performed using a fixed-effect model. In the previous full NMA feasibility assessment, it was noted that due to the inclusion of very few studies in the network, the estimate of between-study variability of treatment effect can be unreliable in random-effect models. Outcomes included in the analysis were PFS and OS. The NMA was performed using WinBUGS (version 1.4.1) with model parameters estimated using Markov chain Monte Carlo techniques. The model was run for 21,000 iterations. The mean and median of the 21,000 iterations were calculated including 95% credibility intervals (Crls) based on the 2.5 and 97.5 percentiles from the distribution of the calculated data. The WinBUGS code was provided.

Results and Conclusions of NMA for Non-Visceral Disease

Results of the NMA are presented in Table 4. Results suggest that the PFS HR and OS HR for fulvestrant versus anastrozole are significantly better. While the PFS HR was in favour of palbociclib plus letrozole compared with fulvestrant and the OS HR was in favour of fulvestrant; neither HRs are statistically significant.

Table 4: Results of NMA[27]

	Mean HR	Median HR	2.5%	97.5%
PFS (fulvestrant versus)				
Anastrozole	0.5956	0.5885	0.4414	0.787
Palbociclib + letrozole	1.732	1.635	0.8437	3.17
OS (fulvestrant versus)				
Anastrozole	0.6525	0.6391	0.437	0.9429
Palbociclib + letrozole	0.849	0.7986	0.4086	1.561

The manufacturer's overall conclusions were that the NMA were based on the pooled HR reported within clinical trials that provide a comparison of fulvestrant OS and PFS to that of palbociclib plus letrozole. The methods relied on proportional hazards assumptions and assumed equivalent clinical efficacy of anastrozole and letrozole.

Critical Appraisal of the NMA for Non-Visceral Disease

The quality of the NMA was assessed according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons. Details of the critical appraisal are presented in Table 5.

Table 5: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†

ISPOR Questions	Details and Comments‡
1. Is the population relevant?	**Yes, in part.** The indication for this review was to assess the efficacy and safety of fulvestrant for hormonal treatment of non-visceral locally advanced or metastatic HER2- breast cancer in postmenopausal women, regardless of age, who have not been previously treated with endocrine therapy. The study populations in FALCON, FIRST, and PALOMA-1 consisted of locally advanced or metastatic HER2- breast cancer in postmenopausal women; however, none of the trials were limited to non-visceral disease and only one (FALCON) was limited to no prior endocrine therapy.
2. Are any critical interventions missing?	No. For the focus of this NMA, the Manufacturer included all relevant interventions for this patient population.
3. Are any relevant outcomes missing?	**Yes, in part.** PFS and OS are relevant outcomes reported in the NMA. HrQoL, ORR, DoR, CBR, and safety outcomes are other relevant outcomes but were not considered in the NMA.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Yes. The settings and circumstances of the three included trials were applicable to the population under review.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes. The search strategy for the full NMA was provided. Multiple databases (e.g., MEDLINE, EMBASE, and Cochrane Central Registry of Trials) were searched. Additional steps (e.g., bibliographies of relevant systematic reviews, conference meetings) to identify studies were made. Selection criteria were listed. However, it was not reported whether they performed screening calibration exercises and a risk of bias assessment.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**Unclear.** The trials for the interventions of interest form one connected network under the assumption of equivalence of anastrozole and letrozole.
7. Is it apparent that poor quality studies were included thereby leading to bias?	**Unclear.** The Manufacturer reported the use of the National Institute for Health and Care Excellence checklist as well as a grade for allocation concealment and Jadad score. An overview of the assessment was provided. The Manufacturer stated that the overall risk of bias was low in terms of baseline comparability, statistical

ISPOR Questions	Details and Comments‡
	analyses, and randomization. Of note, there was high risk of bias for blinding for FIRST and PALOMA-1.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**Unclear.** The Manufacturer reported that for 81.8% of studies, information regarding outcome selection and reporting was not clear. Unclear was reported for PALOMA-2, but not for the other three trials included in the non-visceral disease NMA.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	No. The pCODR Methods Team and Clinical Guidance Panel felt there were no major systematic differences in treatment effect modifiers across the different treatment comparisons in the network. Overall, the Clinical Guidance Panel felt studies included were comparable in terms of baseline characteristics. Of note, FALCON and FIRST varied in study design with respect to blinding, phase, and primary outcome.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Not applicable.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Yes. Bayesian ITC was performed.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	**Not applicable.** This was not a closed loop network.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Not applicable.** This was not a closed loop network.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**Yes, in part.** PALOMA-1 was not included in the network of trials as the patient population did not contain at least 65% of relevant patients across each category. However, it was not reported how the 65% criteria was determined and whether it was pre-specified. Sensitivity analyses were not performed; however, the structure of the evidence network (i.e., the presence of several single-study connections between interventions) may preclude analyses.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes, in part.** No rationale was reported for the use of a fixed effect model. In the previous full NMA feasibility assessment, it was noted that due to the inclusion of very few studies in the network, the estimate of between-study variability of treatment effect can be unreliable in random-effect models.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Not applicable.** A fixed effects model was used.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**No.** Subgroup analyses or meta-regression analyses were not performed; however, the Methods Team does recognize that assessment of heterogeneity may have been difficult due to the structure of the evidence network (i.e., the presence of several single-study connections between interventions) and limited number of studies included in the NMA.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes. Refer to Figure 1.
19. Are the individual study results reported?	Yes. A table reporting the baseline characteristics of the trials used in the NMA as well as the effect estimates of PFS and OS. Refer to Table 1 and 2.

ISPOR Questions	Details and Comments‡
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	Yes. The results of the direct comparisons were reported separately from results of the indirect comparisons. Refer to Table 2.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes. Pairwise comparisons from the fixed-effects model were reported in terms of summary hazard ratios and 95% credible interval.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**No.**
23. Is the impact of important patient characteristics on treatment effects reported?	**No.** The impact of important patient characteristics on treatment effects were not reported.
24. Are the conclusions fair and balanced?	**Yes.** The NMA report provided by the Manufacturer did not make any strong conclusions in their report. The NMA performed by the manufacturer showed that the PFS HR and OS HR for fulvestrant versus anastrozole were significantly better. However, while the PFS HR was in favour of palbociclib plus letrozole compared with fulvestrant and the OS HR was in favour of fulvestrant; neither HRs are statistically significant. In addition, the assumption of proportional hazards was not tested for PALOMA-1 and in order to conduct the indirect comparison, it was assumed equivalence of anastrozole to letrozole. The Manufacturer did not include other patient important outcomes in their indirect comparison, and therefore, it is difficult to determine the overall benefit of this drug as compared to palbociclib plus letrozole.
25. Were there any potential conflicts of interest?	**Not reported**
26. If yes, were steps taken to address these?	**Not applicable.**
† Adapted from Jansen et al[33] ‡Bolded comments are considered a weakness of the ITC.	

7.1.3 Summary and Interpretation

Overall, details of the underlying systematic review methodology (searches, study selection, data extraction, critical appraisal, etc.) were provided for the full NMA. However, for the non-visceral disease subgroup NMA, no further methodology is reported except that trials were selected if they included fulvestrant or palbociclib plus letrozole.

The validity of an NMA are based on three assumptions: homogeneity, similarity, and consistency (i.e., were the results from trials on the same comparison homogeneous or heterogeneous; were these trials similar across comparisons enough to consider together; and were the results from direct and indirect comparisons consistent). Heterogeneity was not explored in the form of sensitivity analyses and meta-regression analyses could not be performed due to the small number of studies. Similarity was explored in the submitted NMA in the form of collection of information (i.e., study design and patient characteristics) and consideration of whether the studies appeared similar enough to be compared. The full NMA included details on study design and patient characteristics, the non-visceral disease subgroup NMA had no details on study design and limited on patient characteristics. Upon review, the Methods Team and CGP agreed that the studies appear similar enough to be compared. Lastly, consistency could not be assessed because the network was not a closed loop; therefore, among the pairwise comparison, no direct evidence was available to compare with indirect evidence.

The pCODR Methods Team and Clinical Guidance Panel felt it was appropriate to assume equivalence of anastrozole to letrozole. However, it is unknown whether the proportional hazards

assumption is met for PALOMA-1. Results of the NMA suggested that fulvestrant compared to anastrozole had significantly improved PFS as well as OS; however, both FIRST and FALCON reported non-significant results for OS. It is important to note that the OS data for FIRST and FALCON are not mature as median OS have not been reached.

Conclusion

The Manufacturer submitted a NMA comparing fulvestrant to palbociclib plus letrozole. Details of the underlying systematic review methodology were provided for the full NMA. However, for the non-visceral disease subgroup NMA, no further methodology is reported except that trials were selected if they included fulvestrant or palbociclib plus letrozole. Based on the limited reporting on the methodology for the subgroup NMA, critical appraisal of the submitted NMA was limited by the lack of information. The results of the NMA indicated that treatment with fulvestrant compared to palbociclib plus letrozole were not statistically significant for PFS and OS. Treatment with fulvestrant compared to anastrozole statistically improved PFS and OS. Studies appeared similar enough to be compared. In order to conduct the indirect comparison, it was assumed equivalence of anastrozole to letrozole, this was considered reasonable. However, the assumption of proportional hazards was not tested for PALOMA-1. The results of the NMA should be viewed in light of these underlying assumptions (AIs have similar efficacy, definition of non-visceral, and assumption of proportional hazards) used to conduct this analysis. Overall, given these assumptions and the limited reporting on the methodology for the subgroup NMA, the comparative efficacy of fulvestrant to palbociclib plus letrozole is uncertain. This appears to align with the reported results of the NMA which indicate that treatment with fulvestrant compared to palbociclib plus letrozole were not statistically significant for PFS and OS; results demonstrated a lack of direction of treatment effect in favour of one treatment over the other.

8 COMPARISON WITH OTHER LITERATURE

No comparison with other literature was addressed in this review.

9 ABOUT THIS DOCUMENT

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

ppCODR 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. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

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

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

APPENDIX A: LITERATURE SEARCH STRATEGY

See Appendix B for more details on literature search methods.

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials June 2017, Embase 1974 to 2017 July 25, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Line #	Searches	Results
1	(Faslodex* or fulvestrant* or HSDB7658 or HSDB 7658 or ICI 182 780 or ICI 182780 or ICI182780 or ZD9238 or ZD 9238 or ZM 182780 or ZM182780 or ZD182780 or ZD 182780 or CCRIS 8741 or CCRIS8741 or 22X328ZOC4 or 129453-61-8).ti,ab,kf,kw,hw,rn,nm.	12263
2	exp Breast Neoplasms/	720316
3	exp Breast/ or (breast* or mammar* or nipple*).ti,ab,kw,kf.	1050016
4	exp Neoplasms/ or (neoplasm* or neoplastic or malignan* or carcinoma* or cancer* or tumor* or tumour* or sarcoma*).ti,ab,kw,kf.	8648796
5	2 or (3 and 4)	939864
6	1 and 5	6425
7	6 use pmez	1702
8	6 use cctr	264
9	*fulvestrant/ or (Faslodex* or fulvestrant* or HSDB7658 or HSDB 7658 or ICI 182 780 or ICI 182780 or ICI182780 or ZD9238 or ZD 9238 or ZM 182780 or ZM182780 or ZD182780 or AD 182780 or CCRIS 8741 or CCRIS8741 or ZM182780 or 22X328ZOC4).ti,ab,kw.	8957
10	exp Breast Cancer/	654242
11	exp Breast/ or (breast* or mammar* or nipple*).ti,ab,kw.	1049822
12	exp Neoplasm/ or (neoplasm* or neoplastic or malignan* or carcinoma* or cancer* or tumor* or tumour* or sarcoma*).ti,ab,kw.	8645064
13	10 or (11 and 12)	925682
14	9 and 13	4211
15	14 use oemezd	2445
16	15 and conference abstract.pt.	723
17	limit 16 to yr="2012 -Current"	555
18	15 not 16	1722
19	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.	1069660
20	Randomized Controlled Trial/	934353
21	exp Randomized Controlled Trials as Topic/	256630

22	"Randomized Controlled Trial (topic)"/	132173
23	Controlled Clinical Trial/	535770
24	exp Controlled Clinical Trials as Topic/	267133
25	"Controlled Clinical Trial (topic)"/	9009
26	Randomization/	189118
27	Random Allocation/	185800
28	Double-Blind Method/	387648
29	Double Blind Procedure/	141329
30	Double-Blind Studies/	251609
31	Single-Blind Method/	68525
32	Single Blind Procedure/	28573
33	Single-Blind Studies/	70057
34	Placebos/	312626
35	Placebo/	310933
36	Control Groups/	112350
37	Control Group/	112252
38	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3599892
39	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	715411
40	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2372
41	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.	1347300
42	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	86178
43	allocated.ti,ab,hw.	155756
44	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	96656
45	or/19-44	4553559
46	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study).pt.	1072492
47	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.	847231
48	Multicenter Study.pt.	305474
49	Randomized Controlled Trial/	934353
50	exp Randomized Controlled Trials as Topic/	256630
51	"Randomized Controlled Trial (topic)"/	132173
52	Controlled Clinical Trial/	535770
53	exp Controlled Clinical Trials as Topic/	267133
54	"Controlled Clinical Trial (topic)"/	9009

55	Clinical Studies as Topic/	154662
56	Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/	1512807
57	Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/	332175
58	"Clinical Trial (topic)"/ or "Phase 2 Clinical Trial (topic)"/ or "Phase 3 Clinical Trial (topic)"/ or "Phase 4 Clinical Trial (topic)"/	125616
59	Multicenter Study/ or Multicenter Study as Topic/ or "Multicenter Study (topic)"/	418410
60	Randomization/	189118
61	Random Allocation/	185800
62	Double-Blind Method/	387648
63	Double Blind Procedure/	141329
64	Double-Blind Studies/	251609
65	Single-Blind Method/	68525
66	Single Blind Procedure/	28573
67	Single-Blind Studies/	70057
68	Placebos/	312626
69	Placebo/	310933
70	Control Groups/	112350
71	Control Group/	112252
72	Cross-Over Studies/ or Crossover Procedure/	126839
73	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3599892
74	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	715411
75	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2372
76	(control* adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	7552381
77	(clinical adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	5629981
78	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	86178
79	(phase adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	416763
80	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	168504
81	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	614017
82	allocated.ti,ab,hw.	155756
83	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	96656
84	trial.ti,kf,kw.	746932
85	or/46-84	12450000
86	exp animals/	45435938

87	exp animal experimentation/	2132813
88	exp models animal/	1564264
89	exp animal experiment/	2132813
90	nonhuman/	5231402
91	exp vertebrate/	44180934
92	animal.po.	0
93	or/86-92	46997783
94	exp humans/	36312563
95	exp human experiment/	390180
96	human.po.	0
97	or/94-96	36314109
98	93 not 97	10684696
99	85 not 98	10024147
100	(7 or 18) and 45	449
101	17 and 99	276
102	100 or 8	713
103	remove duplicates from 102	495
104	101 or 103	771
105	limit 104 to english language	699

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#8	Search #7 AND publisher[sb] Filters: English	30
#7	Search #4 AND (#5 OR #6) Filters: English	1581
#6	Search (Breast[Mesh] OR breast[tiab] OR breasts[tiab] OR mammar*[tiab] OR nipple*[tiab]) AND (Neoplasms[Mesh] OR neoplasm*[tiab] OR neoplastic[tiab] OR malignan*[tiab] OR carcinoma*[tiab] OR cancer*[tiab] OR tumor[tiab] OR tumour[tiab] OR tumors[tiab] OR tumours[tiab] OR tumorous[tiab] OR tumourous[tiab] OR sarcoma*[tiab]) Filters: English	299524
#5	Search Breast Neoplasms[Mesh] Filters: English	217705
#4	Search Fulvestrant[supplementary concept] OR Faslodex*[tiab] OR fulvestrant*[tiab] OR HSDB7658[tiab] OR HSDB 7658[tiab] OR ICI 182 780[tiab] OR ICI 182780[tiab] OR ICI18278[tiab] OR ZD9238[tiab] OR ZD 9238[tiab] OR ZM 182780[tiab] OR CCRIS	3756

Search	Query	Items found
	8741[tiab] OR CCRIS8741[tiab] OR ZM182780[tiab] OR ZD182780[tiab] OR ZD 182780[tiab] OR 22X328ZOC4[tiab] OR 129453-61-8[rn] Filters: English	

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

4. **Grey Literature search via:**

Clinical trial registries:

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

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

Search: Faslodex / fulvestrant, breast cancer

Select international agencies including:

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

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

Search: Faslodex / fulvestrant, breast cancer

Conference abstracts:

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

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

Search: Faslodex / fulvestrant, breast cancer - last 5 years

Appendix B: DETAILED METHODOLOGY OF LITERATURE REVIEW

Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2017 July 25) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-2017 July 25) via Ovid; The Cochrane Central Register of Controlled Trials (June 2017) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Faslodex, fulvestrant and breast cancer.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of November 2, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium (SABCS) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

REFERENCES

1. Robertson JFR, Bondarenko IM, Trishkina E, Dvorkin M, Panasci L, Manikhas A, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. Lancet. 2016 Dec 17;388(10063):2997-3005.

2. Robertson JF, Llombart-Cussac A, Rolski J, Feltl D, Dewar J, Macpherson E, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. J Clin Oncol. 2009 Sep 20;27(27):4530-5.

3. AstraZeneca response to pCODR checkpoint meeting questions on fulvestrant (Faslodex) for the treatment of locally advanced or metastatic breast cancer [additional manufacturer's information]. Mississauga (ON): AstraZeneca; 2017 Sep 18.

4. Robertson JF, Cheung KL, Noguchi S, Shao Z, Degboe A, Lichfield J, et al. Health-related quality of life from a phase 3 randomized trial of fulvestrant 500 mg vs anastrozole for hormone receptor-positive advanced breast cancer (FALCON). [Internet]. Abstract presented at: American Society of Clinical Oncology Annual Meeting. 2017 Jun 2-6; Chicago, IL. [cited 2017 Aug 17]. Available from: http://meetinglibrary.asco.org/record/144848/abstract

5. Robertson JFR, Noguchi S, Shao Z, Grinsted LM, Fazal M, Ellis MJ. Progression-free survival results in patient subgroups from a Phase 3 randomized trial of fulvestrant 500 mg vs anastrozole for hormone receptor-positive advanced breast cancer (FALCON). Cancer Res [Internet]. 2017 [cited 2017 Aug 3];77(4 Supplement 1). Available from: http://cancerres.aacrjournals.org/content/77/4_Supplement/P2-08-02

6. ICH harmonised tripartite guideline: statistical principles for clinical trials E9 [Internet]. Geneva: International Conference on Harmonisation (ICH); 1998 Feb 5. [cited 2018 Jan 4]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

7. Simon R. Patient subsets and variation in therapeutic efficacy. Br J Clin Pharmacol. 1982 Oct;14(4):473-82. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1427603

8. Sun X, Briel M, Busse JW, You JJ, Akl EA, Mejza F, et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review. BMJ. 2012 Mar 15;344:e1553.

9. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010 Mar 30;340:c117.

10. Appropriate interpretation of subgroup analysis. Ottawa: CADTH; 2013 Jul. (Advancing the Science Brief).

11. Faslodex: EPAR assessment report [Internet]. London: European Medicines Agency (EMA); 2017 May 29. [cited 2017 Oct 30]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000540/WC500235903.pdf

12. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2017 [Internet]. Toronto (ON): Canadian Cancer Society; 2017. [cited 2017 Nov 28]. Available from: http://www.cancer.ca/~/media/cancer.ca/CW/publications/Canadian%20Cancer%20Statistics/Canadian-Cancer-Statistics-2017-EN.pdf

13. Piccart M, Hortobagyi GN, Campone M, Pritchard KI, Lebrun F, Ito Y, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2dagger. Ann Oncol. 2014 Dec;25(12):2357-62.

14. Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. N Engl J Med. 2009 Feb 19;360(8):790-800.

15. Kohler BA, Sherman RL, Howlader N, Jemal A, Ryerson AB, Henry KA, et al. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. J Natl Cancer Inst [Internet]. 2015 Jun [cited 2017 Nov 28];107(6):djv048. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4603551

16. Breast cancer. Version 3. Fort Washington (PA): National Comprehensive Cancer Network; 2017. (NCCN clinical practice guidelines in oncology).

17. Bergh J, Jonsson PE, Lidbrink EK, Trudeau M, Eiermann W, Brattstrom D, et al. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. J Clin Oncol. 2012 Jun 1;30(16):1919-25.

18. Mehta RS, Barlow WE, Albain KS, Vandenberg TA, Dakhil SR, Tirumali NR, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. N Engl J Med [Internet]. 2012 Aug 2 [cited 2017 Nov 28];367(5):435-44. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3951300

19. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016 Nov 17;375(20):1925-36.

20. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med. 2016 Nov 3;375(18):1738-48.

21. Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. J Clin Oncol. 2010 Oct 20;28(30):4594-600.

22. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016 Apr;17(4):425-39.

23. Ellis MJ, Bondarenko I, Trishkina E, Dvorkin M, Panasci L, Manikhas A, et al. FALCON: a phase III randomised trial of fulvestrant 500 mg vs. anastrozole for hormone receptor-positive advanced breast cancer [abstract]. Ann Oncol. 2016;27 Suppl 6. (Presented at European Society for Medical Oncology; 2016 Oct 7-11; Copenhagen, Denmark).

24. Robertson JFR, Cheung K-L, Noguchi S, Shao A, Degboe A, Lichfield J, et al. Health-related quality of life from a phase 3 randomized trial of fulvestrant 500 mg versus anastrozole for homone receptor-positive advanced breast cancer (FALCON). Poster presented at: American Society of Clinical Oncology Annual Meeting. 2017 June 2-6; Chicago, IL.

25. Ellis MJ, Llombart-Cussac A, Feltl D, Dewar JA, Jasiowka M, Hewson N, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: overall survival analysis from the phase II FIRST study. J Clin Oncol [Internet]. 2015 Nov 10 [cited 2017 Aug 3];33(32):3781-7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4737861/pdf/zlj3781.pdf

26. Robertson JF, Lindemann JP, Llombart-Cussac A, Rolski J, Feltl D, Dewar J, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study. Breast Cancer Res Treat. 2012 Nov;136(2):503-11.

27. pan-Canadian Oncology Drug Review manufacturer submission: Faslodex® (fulvestrant) 250 mg/5 mL (50 mg/mL) pre-filled syringe for intramuscular injection. Company: AstraZeneca Canada. Mississauga (ON): AstraZeneca Canada; 2017 Jul 14.

28. AstraZeneca. A global study to compare the effects of fulvestrant and arimidex in a subset of patients with breast cancer. (FALCON). 2012 May 11 [cited 2017 Aug 17; updated 2017 Jun 30]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/study/NCT01602380 NLM Identifier: NCT01602380.

29. AstraZeneca. A clinical trial to compare efficacy and tolerability of faslodex with arimidex in patients with advanced breast cancer (FIRST). 2006 Jan 10 [cited 2017 Aug 17; updated 2017 Feb 1]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/record/NCT00274469 NLM Identifier: NCT00274469.

30. Revised clinical study protocol: A randomised, open-label, parallel-group, multi-centre, phase III study to compare the efficacy and tolerability of fulvestrant (FASLODEX™) 500 mg with anastrozole (AMIMIDEX™) 1 mg as hormonal treatment for postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer who have not previously been treated with any hormonal therapy (FALCON) [Internet]. Cambridge (GB): AstraZeneca; [2013].

31. Revised clinical study protocol: A randomised, open-label, parallel-group, multi-centre, phase II study to compare the efficacy and tolerability of fulvestrant (FASLODEX™) 500 mg with anastrozole (AMIMIDEX™) 1 mg as first line hormonal treatment for postmenopausal women with hormone receptor positive advanced breast cancer. Cambridge (GB): AstraZeneca; [2014].

32. Chinese Academy of Medicine Sciences. Fulvestrant 500mg with exemestane endocrine therapy for postmenopausal advanced breast cancer patients (FRIEND). 2016 Jan 4 [cited 2017 Aug 22]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/study/NCT02646735 NLM Identifier: NCT02646735.

33. Jansen JP, Trikalinos T, Cappelleri JC, Daw J, Andes S, Eldessouki R, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health [Internet]. 2014 Mar [cited 2017 Oct 30];17(2):157-73. Available from: http://www.sciencedirect.com/science/article/pii/S1098301514000126