PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Everolimus (Afinitor) for Advanced Breast Cancer

March 25, 2013

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the effect of everolimus (Afinitor) plus exemestane on patient outcomes compared to placebo plus exemestane in postmenopausal women with HR+, HER2- advanced breast cancer (ABC) after treatment failure with letrozole or anastrozole. Everolimus (Afinitor) is a rapamycin analog and signal transduction inhibitor that selectively inhibits mammalian target of rapamycin (mTOR), a serine-threonine kinase that stimulates cell growth, proliferation and angiogenesis. The recommended dose of everolimus is 10 mg + exemestane (25mg) administered orally once daily.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

BOLERO-2 was an international, multicenter, double-blind, phase 3 randomised controlled trial that compared the safety and efficacy of everolimus plus exemestane (n=485) given orally once daily to placebo plus exemestane (n=239).[1-7] The study recruited postmenopausal women (median age 62 years) with HR+, HER2- ABC who had failed previous treatment with letrozole or anastrozole. Patients were predominantly Caucasians, had visceral involvement and bone metastasis (76%, 56% and 77%, respectively). Most patients were of ECOG performance status of 0 and 1 (60% and 36%, respectively). Patients with a history of brain metastasis, HER2 overexpression, and previous treatment with exemestane or mTOR inhibitors were excluded from the study. This study also did not permit crossover for patients who had progressed on the exemestane alone arm to the combination of everolimus and exemestane.

There is only one phase III study (BOLERO-2) to review with limited follow-up and no overall survival data available at this time. The study design also did not explore the role of combining everolimus with other endocrine therapies. The results of BOLERO-6, a three arm, randomized open label phase II study of everolimus in combination with exemestane versus everolimus alone versus capecitabine in women with locally advanced, recurrent or metastatic breast cancer after recurrence or progression on letrozole or anastrozole will provide further information on the benefit of everolimus compared to alternative therapies.

Efficacy

The primary endpoint was progression free survival (PFS). PFS by investigator assessment in the everolimus plus exemestane and placebo plus exemestane arms were 7.8 months and 3.2 months, respectively [HR 0.45 (95% CI 0.38, 0.54), p<0.0001]. PFS by central radiological assessment was 11.0 months and 4.1 months, respectively [HR 0.38 (95% CI 0.31, 0.48), p<0.0001]. The results for PFS were consistent for all subgroups.

The secondary endpoints included overall survival (OS), health-related quality of life (HRQoL), and clinical benefit rate (CBR). At the cut-off date for final PFS analysis (December 15, 2011), there were 200 deaths, of which 25.4% vs. 32.2% were in the everolimus plus exemestane arm vs. placebo plus exemestane arm, respectively. The final OS analysis will be conducted after 398 deaths have occurred. The median time to definitive deterioration (TTD) in HRQoL for everolimus plus exemestane and placebo plus exemestane arms were 8.3 months and 5.8 months respectively, [HR 0.74 (95% CI 0.58, 0.95), p=0.0084] where the minimal important difference (MID) was set at 5%. At a MID of 10%, TTD was 11.7 months and 8.4 months, respectively, [HR 0.80 (95% CI 0.61, 1.06), p=0.1017]. There was no statistically significant difference in TTD between

treatment groups for any defined subgroups. The clinical benefit rates (CBR) were 33.4% vs.18.0% by investigator assessment and 30.9% vs. 15.1% by central assessment in the everolimus plus exemestane and placebo plus exemestane arms, respectively.

Harms

The most common SAEs reported in the everolimus plus exemestane group were pneumonitis, pneumonia, anemia, dyspnea, pulmonary embolism, pyrexia, and renal failure. There were more AEs leading to discontinuation of therapy in the everolimus plus exemestane group compared with the placebo plus exemestane group (19.1% vs. 4.6%, respectively). As of February 11, 2011, fatal AEs occurred in 1.5% of patients in the everolimus plus exemestane group compared to 0.4% of patients in the placebo plus exemestane group.

1.2.2 Additional Evidence

pCODR received input on everolimus from the following patient advocacy groups, the Canadian Breast Cancer Network and Rethink Breast Cancer. Provincial Advisory group input was obtained from six of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

A meta-analysis of published trials was conducted to evaluate the incidence of pneumonitis in patients treated with mTOR inhibitors for malignancy.[8] Pneumonitis was the most common adverse event of pulmonary toxicity in patients treated with everolimus. The grade 3 and 4 pneumonitis in patients receiving everolimus was 2.4% [RR 8.8 (95% CI 2.4, 32.2); p<0.001]. It was concluded that about 10% of patients treated with mTOR inhibitors may experience pneumonitis that may affect quality of life and disrupt therapy.

An open-label, phase 2 placebo-controlled trial (TAMRAD) was conducted to evaluate the efficacy and safety of everolimus in combination with tamoxifen in patients with HR+, HER2- ABC with prior exposure to aromatase inhibitors. The primary endpoint was CBR at 6 months. Unlike the phase 3 study, this small open label phase 2 study was prone to bias as imbalances between groups were noticed in some areas including hormone receptor status and performance status. The primary endpoint, CBR, was not a direct measure of benefit. Progression was assessed by local investigators that could be highly subjective. Quality of life was not assessed. The results in this study should therefore be considered as hypothesis generating. However, the safety profile of everolimus in this study was similar to that seen in BOLERO-2.

No supplemental questions were addressed in this review.

1.2.3 Interpretation and Guidance

Breast cancer deaths are the second most common cause of cancer mortality in Canadian women with an estimated 5,100 deaths in 2012.[9] Breast cancer deaths also contribute to the greatest potential life years lost from any illness in Canadian women. Although improvement in overall survival is considered to be the primary goal of any cancer therapy, many consider there to be merit in cancer treatments that delay disease progression.[10]

BOLERO-2 is an international phase III placebo controlled trial that compared the use of everolimus with exemestane to exemestane with placebo (patient ratio 2: 1) in women with hormone-sensitive advanced breast cancer who had recurrence after, or progressed while receiving therapy with a non steroidal aromatase inhibitor (letrozole or anastrozole). At the pre-planned interim analysis, the study demonstrated a statistically significant improvement in median progression-free survival of 10.6 months with everolimus and exemestane vs. 4.1 months with placebo and exemestane; HR = 0.36 with 95 % confidence CI 0.27-0.47; p<0.001). These results differ from those reported by local investigators [which was the primary end-point of the study] where progression free survival was reported as 6.9 months in the everolimus/exemestane arm vs. 2.8 months in the exemestane arm (HR=0.43 with 95 % confidence; CI 0.35-0.54; p<0.001). With an

absolute improvement in progression-free survival of 4.1-6.5 months, the magnitude of benefit is both statistically and clinically meaningful. At the time of this interim analysis, 296 patients were still receiving study treatment and 83 deaths had occurred. Overall survival is event driven and the final analysis for OS will not be performed until after 398 deaths have occurred.

The most common grade 3 or 4 toxicities were: stomatitis (8% in combination vs. 1%), anemia (6% vs. < 1%), dyspnea (4% vs. 1%), fatigue (4% vs. 1%) and pneumonitis (3% vs. 0%). Despite the higher incidence of adverse events seen in the combination arm, the time to deterioration of ECOG performance status and time to deterioration of quality of life was not statistically different between the two treatment groups. Although the most common side effects experienced with everolimus plus exemestane in this trial are not life threatening they do require close monitoring by an experienced health care team familiar with the toxicities associated with this combination, as a higher incidence of adverse events may occur in an unselected non- clinical trial population.

To date, there is no randomized phase III data available on the clinical benefit of everolimus in combination with other endocrine therapies (e.g. tamoxifen, fulvestrant) and thus the use of everolimus in combination with other endocrine therapies cannot be endorsed at this time. In the Canadian context, it is likely that the combination of everolimus and exemestane will replace exemestane given as a single agent in the metastatic setting. It is possible that the combination of exemestane and everolimus could be used in the 1st line metastatic setting for patients who have received anastrozole or letrozole in the adjuvant setting (16-21% of BOLERO-2 study population). It is also reasonable to consider this combination in the 2nd or third line or greater setting as this represented the majority of the study population.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to the combination of everolimus and exemestane in the treatment of postmenopausal women with hormone receptor positive , HER 2 negative, metastatic breast cancer who have previously been exposed to a non-steroidal aromatase inhibitor (e.g anastrazole, letrozole) and who have a good performance status (0-2. This recommendation is based on a planned interim analysis of a single phase III randomized placebo-controlled international study (BOLERO-2). While there was a statistically and clinically significant improvement in progression free survival (the primary endpoint of this study), the data are too immature to report on overall survival. The clinical panel acknowledges this recommendation is based on statistical and clinical benefit of PFS and delay in deterioration of QOL. There was however more toxicity associated with the combination of everolimus and exemestane although this did not appear to have a negative impact on quality of life as measured in this study. Patients receiving this therapy should be monitored closely by a health care team familiar with the toxicity profile these agents.

The Clinical Guidance Panel also considered that from a clinical perspective:

- metastatic breast cancer is the second leading cause of cancer death in women and there is a need for new and improved endocrine therapies, both in terms of efficacy and tolerability;
- everolimus in combination with exemestane demonstrated an improvement in median progression free survival (range; 4.6-6.5 months) with a hazard ratio between 0.38-0.45);
- this is aligned with patient values who want access to life extending therapy if it can stop the progression of the disease, even if for a short period of time and even with potential side effects;

- There were more serious adverse events (23% vs. 12%), and there was a higher rate of treatment withdrawals due to adverse events (19% vs. 4%) in the exemestane/everolimus arm compared to the placebo/exemestane arm, respectively.
- Close monitoring by an experienced health care team familiar with the toxicities associated with this combination is needed as a higher incidence of adverse events may occur in an unselected non- clinical trial population
- there are 3 clinical situations where the Clinical Guidance Panel noted there was insufficient evidence to support the use of everolimus and exemestane:
    - Patients with HER2 + disease (not included in the study population)
    - Everolimus in combination with other endocrine therapies (no phase III data)
    - Patients with brain metastases (not included in study population).

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding everolimus (Afinitor) for ABC. 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 pCODR website, www.pcodr.ca.

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

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on everolimus (Afinitor) for ABC and a summary of submitted Provincial Advisory Group Input on everolimus (Afinitor) for ABC are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Everolimus (Afinitor) is a rapamycin analog and signal transduction inhibitor that selectively inhibits mammalian target of rapamycin (mTOR), a serine-threonine kinase that stimulates cell growth, proliferation and angiogenesis. On July 20, 2012, the US FDA[11] has approved everolimus (Afinitor, Novartis) for the treatment of postmenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer (ABC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. On July 26, 2012, the European Medicines Agency (EMA)[6] has approved everolimus for the treatment of HR+, HER2- ABC, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor (NSAI). The approval was based on a phase 3, randomized, double-blind, multicenter trial (the BOLERO-2 study).

The first-line treatment option for patients with HR+ ABC is usually endocrine therapy using NSAIs such as letrozole or anastrozole if no prior exposure to a NSAI in the early stage or advanced stage setting. In patients who experience recurrence with NSAI, a second line treatment option is the use of an alternative aromatase inhibitor such as exemestane, or selected estrogen receptor modulators (SERMS) such as tamoxifen or fulvestrant. Patients, whose tumors progress on all endocrine therapies or with rapidly progressive and/or symptomatic disease, are usually offered treatment with chemotherapy. The recommended dose of everolimus (Afinitor) for the treatment of postmenopausal women with HR+, HER2- ABC is 10 mg, taken once daily.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the efficacy and safety of everolimus in combination with exemestane in postmenopausal women with HR-positive and HER2-negative ABC refractory to NSAIs.

2.1.3 Highlights of Evidence in the Systematic Review

The efficacy and safety of everolimus 10 mg plus exemestane 25 mg (n=485) given once daily were compared with placebo plus exemestane (n=239) in an international, multicenter, double-blind, phase 3 RCT (the BOLERO-2 study).[1-7] The study recruited postmenopausal women (median age 62 years) with HR+, HER2- ABC refractory to previous treatment with letrozole or anastrozole. Patients were predominantly Caucasians (76%), and had visceral involvement (56%) and bone metastasis (77%). Most patients were of ECOG performance status of 0 (60%) and 1 (36%). Patients with a history of brain metastasis, HER2 overexpression, and previous treatment with exemestane or mTOR inhibitors were excluded from the study. The primary endpoint was progression free survival (PFS). The secondary endpoints included overall survival (OS), health-related quality of life (HRQoL), and clinical benefit rate (CBR). Safety outcomes included death due to adverse events (AEs), serious AEs (SAEs), AEs leading to discontinuation, and any AEs. Efficacy was evaluated in 724 patients (full analysis set, ITT) and safety was evaluated in 720 patients (safety analysis set).

At the cut-off date for final PFS analysis (December 15, 2011; 17.7 months), there were 200 deaths, of which 25.4% were in the everolimus plus exemestane arm and 32.2% in the placebo plus exemestane arm. Final OS analysis will be conducted after 398 deaths. PFS by investigator assessment was 7.8 months and 3.2 months in the everolimus plus exemestane and placebo plus exemestane arms, respectively [HR 0.45 (95% CI 0.38, 0.54), p<0.0001]. PFS by central radiological assessment was 11.0 months and 4.1 months, respectively [HR 0.38 (95% CI 0.31, 0.48), p<0.0001]. The results for PFS were consistent for all subgroups.

The median time to definitive deterioration (TTD) in HRQoL was 8.3 months and 5.8 months for everolimus plus exemestane and placebo plus exemestane arms, respectively, [HR 0.74 (95% CI 0.58, 0.95), p=0.0084] when the minimal important difference (MID) was set at 5%. At a MID of 10%, TTD was 11.7 months and 8.4 months, respectively, [HR 0.80 (95% CI 0.61, 1.06), p=0.1017]. There was no statistically significant difference in TTD between treatment groups for any defined subgroups.

The clinical benefit rates (CBR) were 33.4% and 18.0% in the everolimus plus exemestane and placebo plus exemestane arms, respectively, by the investigator assessment; 30.9% and 15.1%, respectively, by central assessment.

The most common grade 1-4 AEs (≥ 10%) suspected to be related to the study drug in patients receiving everolimus plus exemestane were stomatitis, rash, fatigue, decreased appetite, diarrhea, dysgeusia, nausea, pneumonitis, weight loss, epistasis and thrombocytopenia. The most common SAEs reported in the everolimus plus exemestane group were pneumonitis, pneumonia, anemia, dyspnea, pulmonary embolism, pyrexia, and renal failure. There were more AEs leading to discontinuation of therapy in the everolimus plus exemestane group (19.1%) compared with the placebo plus exemestane group (4.6%). As of February 11, 2011, fatal AEs occurred in 1.5% of patients in the everolimus plus exemestane group compared to 0.4% of patients in the placebo plus exemestane group.

Table 1: Key Results from BOLERO-2 Study

Efficacy (cut-off at Dec 15, 2011)				
		Median (months)	**HR (95% CI)**	**P value**
OS	**Everolimus (n=485)**	Immature		
	Placebo (n=239)			
PFS (local)	**Everolimus (n=485)**	7.8		
	Placebo (n=239)	3.2	0.45 (0.38, 0.54)	<0.0001
PFS (central)	**Everolimus (n=485)**	11.0		

Efficacy (cut-off at Dec 15, 2011)				
		Median (months)	**HR (95% CI)**	**P value**
	Placebo (n=239)	4.1	0.38 (0.31, 0.48)	<0.0001
Safety (cut-off at Feb 11, 2011)				
	Everolimus (n=482)		**Placebo (n=238)**	
Deaths, n (%)	51 (10.6)		31 (13.0)	
SAEs, n (%)	110 (22.8)		29 (12.2%)	
AEs leading to discontinuation of treatment, n (%)	92 (19.1)		11 (4.6)	
Any AEs drug-related, n (%)	462 (95.9)		142 (59.7)	

At present, a phase 3b, multi-center, open-label, single-arm study is evaluating the efficacy, safety, quality of life and health resources utilization in postmenopausal women with HR+ breast cancer progressing following prior therapy with NSAIs treated with the combination of everolimus and exemestane. It is estimated to enroll 300 patients. (NCT01626222)

2.1.4 Comparison with Other Literature

Relevant literature identified jointly by the pCODR Clinical Guidance Panel and Methods Team and providing supporting information to the systematic review is summarized below. This information has not been systematically reviewed.

A meta-analysis of published trials was conducted to evaluate the incidence of pneumonitis in patients treated with mTOR inhibitors for malignancy.[8] Five articles retrieved from January 2005 to December 2011 were included for analysis. Of a total of 2,233 patients, 989 had breast cancer (269 localized, 720 advanced), 833 had neuroendocrine tumors, and 411 had metastatic renal cell carcinoma. Pneumonitis was the most common adverse event of pulmonary toxicity in patients treated with everolimus. For all grades, the incidence of pneumonitis was 10.4% in the everolimus arm compared to 0% in the control arm [RR 31.1 (95% CI 8.9, 109.6); p<0.001]. The rate of grade 3 and 4 pneumonitis in patients receiving everolimus was 2.4% [RR 8.8 (95% CI 2.4, 32.2); p<0.001]. Subgroup analysis for type of control used (i.e., active control compared to placebo control) was consistent with the overall analysis. There was no difference in lung metastasis in the everolimus treated patients compared to patients treated in the control arms. It was concluded that about 10% of patients treated with mTOR inhibitors may experience pneumonitis that may affect quality of life and disrupt therapy.

The US FDA has put out warnings and precautions that there have been cases of renal failure (including acute renal failure), some with a fatal outcome, in patients treated with everolimus. [12] The Canadian product monograph contains similar warnings and precautions.[7]

An open-label, phase 2 placebo-controlled trial (TAMRAD) was conducted to evaluate the efficacy and safety of everolimus in combination with tamoxifen in patients with HR+, HER2- ABC with prior exposure to aromatase inhibitors. The study randomized 111 patients into everolimus plus tamoxifen arm (n=54) and tamoxifen alone (n=57). The primary endpoint was CBR at 6 months. Secondary endpoints included TTP, OS, objective response rate (ORR), and toxicity determined by AEs and laboratory measures. The 6-month CBR was 61% and 42% (exploratory p=0.045) in everolimus plus tamoxifen and tamoxifen alone, respectively. Median TTP was 8.6 months and 4.5 months, respectively (HR 0.54; 95% CI 0.36, 0.81; exploratory p=0.002). Median OS was not reached in the everolimus plus tamoxifen group; it was 33.9 months with tamoxifen alone group

(HR 0.45; 95% CI 0.24, 0.81; exploratory p=0.007). The common AEs associated with everolimus plus tamoxifen compared with tamoxifen alone were fatigue (72% vs. 53%), stomatitis (56% vs. 7%), anorexia (43% vs. 18%), and diarrhea (39% vs. 11%). Unlike the phase 3 study, this small open label phase 2 study was prone to bias. Imbalances between groups were noticed in some areas including hormone receptor status and performance status. The primary endpoint, CBR, was not a direct measure of benefit. Progression was assessed by local investigators that could be highly subjective. Quality of life was not assessed. The results in this study should therefore be considered as hypothesis generating. However, the safety profile of everolimus in this study was similar to that seen in the BOLERO-2.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

2.1.6 Other Considerations

Patient Advocacy Group Input

- Patients with stage IV ABC respond differently to treatment and experience many symptoms with disease progression.
- It is important to patients to have access to a variety of therapies that can help manage the progression of their disease, and extend their life expectancy without increasing side effects that will negatively impact their daily lives.
- Patients report their biggest fear following treatment is recurrence and the spread of cancer to other areas of the body.
- The most important treatment aspect for patients is survival. Patients want access to life extending therapy if it can stop the progression of the disease, even if for a short period of time and even with potential side effects.
- There are many financial and psychosocial impacts to patients and their families from an advanced breast cancer diagnosis.
- Although there are promising results with everolimus in BOLERO-2 study, and one of the benefits of everolimus is that it is given orally that the patient can have the treatment at home, the toxicity and side effects are similar to chemotherapy that requires closer monitoring, according to an oncologist.
- The most common side effects of everolimus include mouth sores, infections due to neutropenia, rash, fatigue, diarrhea and decreased appetite. Patients are willing to endure these side effects in order to gain the benefits of prolonged quality of life.

PAG Input

- From a PAG perspective, the implementation of a recommendation for the use of everolimus in combination with exemestane, instead with any aromatase inhibitors, is favourable to a limited population.
- PGA recognized that everolimus may be a convenient option that can be delivered to patients in both rural and urban settings as it is an oral therapy.
- However, PAG noted several barriers to implementation including differences in patient access to oral cancer drug treatment among jurisdictions, the impact of retail pricing of everolimus to treatment costs as all doses of everolimus are priced the same.

- PAG requested clarity regarding the duration of therapy for everolimus plus exemestane. PAG recognized that if therapy is continued until no longer clinically beneficial or until unacceptable toxicity is observed in patients, this could be a potential barrier to implementation as it creates uncertainty regarding budget impact.

Other

- The EMA/CHMP noted that there was a possibility that patients in the control arm in the BOLERO-2 study received suboptimal treatment with exemestane, because of low objective response rate (ORR) in the exemestane treated arm (0.4%) compared to the expected ORR of 15%.

- The EMA/CHMP requested the submission of results of the BOLERO-6 study, which compares everolimus to everolimus plus exemestane to chemotherapy, as condition of marketing authorization.

2.2 Interpretation and Guidance

Burden of Metastatic Breast Cancer

Breast cancer deaths are the second most common cause of cancer mortality in Canadian women with an estimated 5,100 deaths in 2012.[9] Breast cancer deaths also contribute to the greatest potential life years lost from any illness in Canadian women. Though improvement in overall survival is considered; by women with breast cancer, health professionals and regulatory bodies; to be the primary goal of any cancer therapy, many consider there to be merit in cancer treatments that delay disease progression.[10] Importantly, patients want access to life extending therapy if it can stop the progression of the disease, even if for a short period of time and even with potential side effects. (PAG input)

Effectiveness of Everolimus

BOLERO-2 is an international phase III placebo controlled trial that compared the use of exemestane (25 mg/day) and everolimus (10 mg/day) to exemestane (25 mg/d) and placebo (ratio 2: 1) in women with hormone-sensitive advanced breast cancer. The study population (N=724) included women who had progressed while receiving therapy with a non steroidal aromatase inhibitor (letrozole or anastrozole) for either early (during or within 12 months of completing adjuvant therapy) or advanced stage disease (during or within 1 month of completing therapy for advanced disease (or both).

The primary clinical end-point was progression-free survival with a number of secondary endpoints including: overall survival, response rate, and safety. At the pre-planned interim analysis, the study demonstrated a statistically significant improvement in median progression-free survival of 10.6 months with everolimus and exemestane vs. 4.1 months with placebo and exemestane; HR = 0.36 with 95 % confidence CI 0.27-0.47; p<0.001). These results differ from those reported by local investigators [which was the primary end-point of the study] where progression free survival was reported as 6.9 months in the everolimus/exemestane arm vs. 2.8 months in the exemestane arm (HR=0.43 with 95% confidence; CI 0.35-0.54; p<0.001). Data for patients who came off study due to disease progression was based on the last valid radiological assessment (which may have

occurred after starting their next therapy). This may account for at least some of the differences seen in progression free survival between investigators and the independent review assessors.

With an absolute improvement in progression-free survival of 4.1-6.5 months, the magnitude of benefit is both statistically and clinically meaningful. At the interim analysis cut off date, 71.5% of patients had discontinued trial therapy in the everolimus and exemestane arm compared to 90% in the placebo/exemestane arm mainly due to disease progression (51.8% everolimus/exemestane vs. 82.8% exemestane/placebo). It is too early to determine if these improvements will translate into improvements in overall survival. At the time of this interim analysis, 296 patients were still receiving study treatment and 83 deaths had occurred. Overall survival is event driven and the final analysis will not be performed until after 398 deaths.

The study was conducted in the appropriate population of women with relative endocrine sensitive advanced breast cancer who had previously been exposed to a non-steroidal aromatase inhibitor. The majority of women (84%) had shown previous sensitivity to endocrine therapy, had a good performance status and had a median disease free interval of close to 5 years. The study was conducted with an appropriate comparator (exemestane) for this patient population and the study design (placebo-controlled) removed elements of investigator bias.

Safety of Exemestane

There were more serious adverse events (23% vs. 12%), and there was a higher rate of treatment withdrawals due to adverse events (19% vs. 4%) in the exemestane/everolimus arm compared to the placebo/exemestane arm, respectively. The most common grade 3 or 4 toxicities were: stomatitis (8% in combination vs. 1%), anemia (6% vs. < 1%), dyspnea (4% vs. 1%), fatigue (4% vs. 1%) and pneumonitis (3% vs. 0%). Despite the higher incidence of adverse events seen in the combination arm, the time to deterioration of ECOG performance status and time to deterioration of quality of life was not statistically different between the two treatment groups. Although the most common side effects demonstrated in this trial are not life threatening (e.g. stomatitis, anemia, dyspnea, hyperglycemia, and fatigue), they do require close monitoring by an experienced health care team familiar with the toxicities associated with this combination, as a higher incidence of adverse events may occur in an unselected non- clinical trial population. In the rare, but potentially life threatening toxicity of pneumonitis, awareness of this adverse effect is also required.

In the combination arm 7 deaths (one death due to stroke and one death due to suicide) attributed to adverse events were reported during or within 28 days after stopping treatment, compared to 1 death in the exemestane only group.

Limitations of Study

There is only one phase III study (BOLERO-2) to review. The results of this interim analysis study demonstrated that everolimus in combination with exemestane provide clinically meaningful improvement in progression-free survival; however, there is limited follow-up and no overall survival data available at this time. The study design did not explore the role of combining everolimus with other endocrine therapies.

The clinical guidance panel determined that it was reasonable to consider exemestane as a comparator treatment, however other treatment options for this population include: chemotherapy (e.g. vinorelbine, gemcitabine, capecitabine, eribulin), tamoxifen, or fulvestrant. The results of BOLERO-6, a three arm, randomized open label phase II study of everolimus in combination with exemestane vs. everolimus vs. capecitabine in women with locally advanced or

metastatic breast cancer who have progressed on letrozole or anastrozole, will provide further information on the benefit of everolimus compared to alternative therapies.

The BOLERO-2 study did not permit crossover for patients who had progressed on the exemestane alone arm to the combination of everolimus and exemestane. This would not have impacted the primary outcome of progression free survival and would have provided important clinical information on the reversibility of endocrine resistance.

Several populations of women were excluded from the BOLERO-2 study. In particular, patients with endocrine sensitive metastatic breast cancer with HER2/neu amplification were excluded from participation. While HER2 targeted therapies have been the mainstay of treatment for this patient population, it would not be unreasonable to offer endocrine therapy alone to patients with endocrine sensitive low burden disease. Patients with brain metastases were also excluded and one could argue that there is a small population of women with endocrine sensitive metastatic breast cancer with stable brain metastases who might potentially benefit from endocrine treatment.

Need and Therapeutic Options

The strength of the combination of everolimus and exemestane as it has been studied to date is the improvement in progression free survival in women with advanced endocrine sensitive breast cancer exposed to non-steroidal aromatase inhibitors.

Based on the currently available data, everolimus in combination with exemestane should be considered in women with hormone receptor positive metastatic breast cancer who have progressed on a non-steroidal aromatase inhibitor (e.g. letrozole or anastrozole). The vast majority of patients (85 % of population) had prior sensitivity to endocrine therapy (as judged by local investigator).

To date, there is no randomized phase III data available on the clinical benefit of everolimus in combination with other endocrine therapies (e.g. tamoxifen, fulvestrant) and thus the use of everolimus in combination with other endocrine therapies cannot be endorsed at this time. In the Canadian context, it is likely that the combination of everolimus and exemestane will replace exemestane given as a single agent in the metastatic setting. This combination should be limited to patients with good performance status (0-1) and administered under close supervision by a knowledgeable health care team of the toxicity profile of the combination of everolimus and exemestane.

It is possible that the combination of exemestane and everolimus could be used in the 1st line metastatic setting for patients who have received anastrozole or letrozole in the adjuvant setting (16-21% of study population). It is also reasonable to consider this combination in the 2nd or third line or greater setting as this represented the majority of the study population.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to the combination of everolimus and exemestane in the treatment of postmenopausal women with hormone receptor positive, HER 2 negative, metastatic breast cancer who have previously been exposed to a non-steroidal aromatase inhibitor (e.g anastrazole, letrozole) and who have a good performance status (0-2). This recommendation is based on a planned interim analysis of a single phase III randomized placebo-controlled International study (Bolero-2). While there was a

statistically and clinically significant improvement in progression free survival (the primary endpoint of this study), the data is too immature to report on overall survival. The clinical panel acknowledges this recommendation is based on statistical and clinical benefit of PFS and delay in deterioration of QOL. There was however more toxicity associated with the combination of everolimus and exemestane although this did not appear to have a negative impact on quality of life as measured in this study. Patients receiving this therapy should be monitored closely by a health care team familiar with the toxicity profile these agents.

The Clinical Guidance Panel also considered that from a clinical perspective:

- metastatic breast cancer is the second leading cause of cancer death in women and there is a need for new and improved endocrine therapies, both in terms of efficacy and tolerability
- everolimus in combination with exemestane demonstrated an improvement in median progression free survival (range; 4.6-6.9 months) with a hazard ratio between 0.38-0.45);
- this is aligned with patient values who want access to life extending therapy if it can stop the progression of the disease, even if for a short period of time and even with potential side effects
- there were more serious adverse events (23% vs. 12%), and there was a higher rate of treatment withdrawals due to adverse events (19% vs. 4%) in the exemestane/everolimus arm compared to the placebo/exemestane arm, respectively
- close monitoring by an experienced health care team familiar with the toxicities associated with this combination is needed as a higher incidence of adverse events may occur in an unselected non- clinical trial population
- there are 3 clinical situations where the Clinical Guidance Panel noted there was insufficient evidence to support the use of everolimus and exemestane:
    - Patients with HER2 + disease (not included in the study population)
    - Everolimus in combination with other endocrine therapies (no phase III data)
    - Patients with brain metastases (not included in study population)

3 BACKGROUND CLINICAL INFORMATION

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

3.1 Description of the Condition

Breast cancer is the most commonly diagnosed malignancy in Canadian women with an estimated incidence of 23,600 new cases and an estimated 5,100 deaths in 2012.[9] While many women diagnosed with early stage breast cancer will be cured of their disease, some women will experience a relapse (spread to other organs) of their disease or present with de novo metastatic breast cancer. While metastatic breast cancer is treatable, it is not curable, with an estimated median life expectancy of 18-24 months.[13]

The goals of systemic therapy in the treatment of metastatic breast cancer are to improve overall survival and to maintain and/or improve quality of life. Systemic therapy may consist of cytotoxic chemotherapy and/or targeted therapy and/or endocrine therapy. The selection of treatment(s) is determined by the biological characteristics of the tumour in addition to the disease burden/pace of disease, performance status, co-morbidities and patient choice.

Endocrine therapy is an integral part of systemic therapy for patients with hormone-receptor positive metastatic breast cancer. Tamoxifen, a selective estrogen receptor modulator, has been shown to provide clinical benefit in both pre- and post-menopausal women with metastatic breast cancer.[14] Aromatase inhibitors prevent the conversion of androstenedione to estradiol in peripheral tissues (e.g. fat, adrenals) in post-menopausal women and have been shown to be effective in women with advanced endocrine sensitive breast cancer.

Unfortunately not all patients will respond to first line endocrine therapy (primary or de novo resistance). In addition, patients who do respond initially to endocrine manipulation will eventually develop progressive disease (acquired or secondary resistance). Upon disease progression, second-line treatment options include other classes of aromatase inhibitors (steroidal or non-steroidal) or other estrogen receptor modulators (tamoxifen) or estrogen receptor down-regulators (fulvestrant). While a significant number of women will experience some degree of clinical benefit from 2nd and even 3rd line endocrine therapy, all women will eventually develop progressive disease. There is clearly a need to develop novel agents to prevent or delay endocrine therapy resistance.

3.2 Accepted Clinical Practice

The treatment of metastatic breast cancer involves systemic therapy (e.g. endocrine therapy, chemotherapy and targeted therapy), supportive therapies (e.g. analgesics, anti-nausea agents, anti-bone resorptive agents and steroids), radiation therapy, surgery (e.g. spinal cord compression, hip fractures) and access to a palliative care allied health service team. The use of treatment modalities will vary by patient and depend on the patients' disease characteristics, comorbidities, preferences, physician recommendations and the availability of treatment options.

While there is no standard algorithm rigorously adhered to in the treatment of metastatic breast cancer, the literature has defined general concepts and principles. Chemotherapy is the preferred treatment option for patients with endocrine insensitive (estrogen receptor negative) and/or high

burden disease (e.g. visceral metastases) or rapidly progressive symptomatic disease. Endocrine therapy is the backbone of treatment for patients with endocrine sensitive disease; particularly those patients with a low burden of disease (e.g. bone only and or soft tissue only disease). For many years, tamoxifen has been considered the "gold" standard in the management of endocrine sensitive metastatic breast cancer. Subsequently, several phase III RCTs have demonstrated the superiority of aromatase inhibitors in women with advanced breast cancer with improvements in progression free survival,[15,16] but not necessarily overall survival. Despite the clinical efficacy of these agents, resistance to this treatment modality is inevitable. Thus, new therapeutic strategies that enhance the efficacy of endocrine therapies are needed.

An emerging mechanism of endocrine resistance is aberrant signalling through the PI3K-Akt-mTOR signalling pathway.[17,18] Growing evidence supports cross-talk between the mTOR pathway and ER signalling. Everolimus (Afinitor) is an mTOR inhibitor that, in pre-clinical models in combination with exemestane, has shown synergistic inhibition of proliferation and induction of cell death. Subsequently, a randomized phase II study comparing everolimus plus letrozole vs. letrozole alone in patients with newly diagnosed ER-positive breast cancer, demonstrated a higher response rate and fall in proliferation marker (Ki67) for the combination than for letrozole alone.[19]

The potential benefit of combining an mTOR inhibitor with an AI was tested in a phase III randomized (2:1), double-blind, placebo-controlled study (BOLERO-2) of exemestane/everolimus vs. exemestane/placebo in post-menopausal women with endocrine sensitive breast cancer that had progressed on an aromatase inhibitor (either letrozole or anastrozole). The median progression free survival (the primary endpoint of the study) at the first interim analysis was 10.6 months for the combination arm vs. 4.1 months for the exemestane arm (based on central assessment) (HR = 0.36, P<0.001).[1] Overall survival, a secondary endpoint, is not available and will be reported when more mature data is available.

While, clinical trials have clearly demonstrated the benefit of aromatase inhibitors, it is important to examine the toxicities experienced by patients on these trials and their impact on quality of life. In BOLERO-2 a higher percentage of patients discontinued combination therapy compared to everolimus alone (19% vs. 4%) due to adverse events although the time to deterioration of ECOG performance status and time to deterioration in quality of life (≥ 5 %) were not statistically different between the 2 treatment arms.

3.3 Evidence-Based Considerations for a Funding Population

The evidence based population suitable for consideration of everolimus for the treatment of hormone receptor positive MBC would be the same population included in the clinical trial (BOLERO-2).

This would include post-menopausal women with hormone receptor positive, HER2 negative metastatic breast cancer that have progressed on letrozole or anastrozole, defined as recurrence during or within 12 months after the end of adjuvant treatment or progression during or within 1 month after the end of treatment for advanced disease. Other previous endocrine therapies (e.g. tamoxifen) and a single prior chemotherapy regimen for advanced disease were allowed. Patients had a good performance status (ECOG 0-2). Patients were excluded if they had a history of brain metastases or previous treatment with exemestane or mTOR inhibitors. Treatment with exemestane +/- everolimus continued until disease progression, unacceptable toxicity or patient or physician recommendation.

It is likely that everolimus, in combination with exemestane, will be used in the 2nd or 3rd line metastatic setting, after exposure to a non-steroidal aromatase inhibitor (anastrozole or letrozole) and/or tamoxifen (in either the adjuvant and/or advanced setting). This is in keeping with the BOLERO-2 study population in which women received a median of 3 previous therapies (including adjuvant). All patients were exposed to a non-steroidal aromatase inhibitor (letrozole or anastrozole) and just under half (47-49 %) had been exposed to tamoxifen (adjuvant or metastatic) and 16-17% to fulvestrant. Patients who were previously exposed to exemestane were excluded from BOLERO-2 and as such these patients should not be included in the recommended population.

It is important to realize that in clinical practice, those patients who initially respond but eventually progress on everolimus and exemestane may be offered further endocrine manipulation (e.g. fulvestrant) depending on duration of response, disease burden and patient preferences.

3.4 Other Patient Populations in Whom the Drug May Be Used

It is not unreasonable to consider the use of everolimus in combination with exemestane for patients who develop recurrent disease while on an adjuvant non-steroidal aromatase inhibitor (i.e. first line metastatic setting).

There is no data to support the use of exemestane and everolimus in patients with brain metastases or those with hormone receptor positive, HER 2 positive metastatic disease (not included in study population). Further studies are warranted in these patient populations.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy groups provided input on everolimus (Afinitor) for advanced breast cancer and their input is summarized below:

- Canadian Breast Cancer Network
- Rethink Breast Cancer

The Canadian Breast Cancer Network obtained information about the patient and caregiver experience related to the medical condition through a variety of sources including: a conversation between the Canadian Breast Cancer Network staff, their Board and a Canadian oncologist with experience treating patients with everolimus; personal experience from a patient who is currently using everolimus; and from published literature.

Rethink Breast Cancer gathered information through discussions with members of its Scientific Advisory Council comprised of oncologists, including one oncologist with experience treating patients with everolimus and patient groups that work in the field of breast cancer. In addition, they also obtained information through printed literature.

From a patient perspective, access to additional therapies that will stop progression of the disease, even if only for a short amount of time, is an important aspect when consideration is given to treatment. Because there is no cure for advanced breast cancer, patients are looking for treatments with manageable side effect profiles that will extend life expectancy while offering an acceptable quality of life. Patient input also indicated that patients would like access to oral treatments for ease of use and the ability to take at home, rather than travelling to a hospital.

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

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with advanced breast cancer

Advanced breast cancer affects all aspects of a patient's life, not only on a physical level but also on a psychosocial level. The experience of a stage IV diagnosis is different for every patient. Some patients respond well to treatment and their disease does not progress for many years, for others the disease may be active sometimes, and for other patients the disease may progress more rapidly.

Patients with advanced breast cancer may experience many symptoms with disease progression. There can be significant pain, numbness, broken bones, weakness, fatigue and nausea, all of which can impact a patient's daily life and negatively affect their quality of life. Treatment is required for each of these symptoms which may be difficult to access. It is important for patients to have access to a variety of therapies that can help manage the progression of their disease.

Additionally the threat of the disease continuing to progress and eventually ending the life of a patient can cause significant fear, anxiety and depression. Rethink Breast Cancer undertook a National Need's Assessment which surveyed 574 Canadian women diagnosed with breast cancer during the last five years. Respondents to the survey indicated their biggest fear following treatment is recurrence and the spread of cancer to other areas of the body.

When advanced breast cancer is progressing and it is not being controlled through treatment there can be several limitations, both physical and psychosocial, for a patient. However, when the disease is controlled, patients are often able to return to their lives and continue the essential role that they provide within their families, work and communities. From a patient perspective, it is very important for patients to have access to therapies that will extend their life expectancy without increasing side effects that will negatively impact their daily lives.

1.1.2 Patients' Experiences with Current Therapy for advanced breast cancer

Input from patient advocacy groups indicates there are currently a variety of different therapies available for the treatment of advanced breast cancer. Most patients with HER2-negative, hormone-receptor positive advanced breast cancer are treated with chemotherapy, radiation and aromatase inhibitors. Current breast cancer treatments work differently in each patient, some work for longer periods of time with minimal side effects while the same therapy may not work for another patient or the patient may experience many of the side effects that can impact their quality of life. Although patients understand there is no cure for advanced breast cancer, it is very important for patients to have access to as many treatment options as possible to slow down the progression of their disease.

The majority of patients with metastatic breast cancer expressed to the Canadian Breast Cancer Network that the most important aspect to patients is survival. If a therapy can stop the progression of the disease, even if only for a short amount of time and even with potential adverse side effects patients want access to life extending treatments. Once a treatment option eventually stops working it is important to patients that there continues to be other options to manage the progression of their disease.

Although there continues to be increased access to therapies for patients with hormone receptor positive advanced breast cancer, it is necessary to ensure that these patients have access to as many options as possible that can assist with slowing the progression of their disease. Often patients with advanced breast cancer rely on accessing clinical trials to help manage their disease. Participation in clinical trials is not always available depending on where patients live and/or receive treatment.

There are many financial implications to the patient and families that are affected by an advanced breast cancer diagnosis. Patients are often off work for a prolonged period of time, reducing their overall income; the full cost of all medications is not always covered; frequent travel for treatment can add an increased financial burden to the patient and their caregiver as well. Oral treatments that can be taken at home and do not require travel to a hospital are preferred.

4.1.3 Impact of advanced breast cancer and Current Therapy on Caregivers

Input from the patient advocacy groups indicate that the impact this cancer has on caregivers can be quite significant since the patient is continuously on treatment. These results in more medical appointments and caregivers often miss work to travel with a patient to appointments and for treatment. Often time's side effects of therapies decrease the patient's ability to participate in their daily routine and increase the responsibilities of the caregiver and due to the lack of the patients' ability to work in the same capacity prior to their diagnosis; the financial burden may be increased on the caregiver. In addition, caregivers often experience psychosocial effects when dealing with a loved one who is terminally ill and the additional responsibility of being a caregiver.

As with patients, a significant challenge for caregivers in regards to current therapy is that eventually a therapy will stop working and other options will be required to continue to slow the progression of the disease. If there is limited access to new therapies, or substantial costs associated with these new therapies that could help manage advanced breast cancer this will create significant challenges to both the patient and the caregiver. When treatment is administered in a hospital setting, caregivers often will accompany the patient and need to rearrange their schedule to fit treatment schedules. According to the National Need's Assessment of 574 patients undertaken by Rethink Breast Cancer the average distance from a patient's home to the hospital is 46 kilometers. Of the patients who travelled to hospital for treatment, 86% of patients were accompanied by someone and 72% of the support during treatment was from a spouse or partner. One of the benefits of everolimus is that it is an oral application which can be taken at home, diminishing the time and cost of travel for patients and their caregivers.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with everolimus (Afinitor)

Both patient advocacy groups indicated that patients are seeking treatments which can extend their life expectancy, even if only for a short period of time. In addition, treatments with manageable side effect profiles that would not affect a patient's daily life would also be considered favorable to patients. Advanced breast cancer patients agree that the opportunity to have more time with family and friends far outweighs the risks in

treatment for this disease. Everolimus has shown to be effective in prolonging progression free survival for postmenopausal women.

Although progression free survival is important to patients, toxicity and quality of life are also a high priority. The Canadian Breast Cancer Network spoke to an oncologist that stated that although there are promising results with everolimus, the toxicity is not insignificant with side effects similar to chemotherapy. One of the noted benefits of everolimus is that, as an oral medication, patients are able to take treatment at home; however, because there are chemo-like side effects closer monitoring is required. Due to the necessity for close monitoring there may still be a need for patients to meet with their oncologist on a more regular basis.

Even though there are side effects worth noting in regards to everolimus and there may be patients who decide the toxicity is too high to manage, the majority (81 %) of patients in the BOLER0-2 clinical trial continued taking Afinitor until the disease started to progress. Stopping the progression of the disease is the primary concern of patients with advanced breast cancer. Patients are often willing to accept the side effects of treatment providing that it stops the progression of the cancer.

A Canadian oncologist that was interviewed by Rethink Breast Cancer who had several patients in the last six months who were administrated this line of therapy. The results of treatment varied: two (2) patients decided to end treatment because of side effects, two (2) ended treatment because of disease progression, one (1) patient is responding very well to the therapy while two (2) others are waiting for further testing of disease progression but are responding well overall. Based on the observations from this oncologist side effects were almost immediately experienced (within the first two weeks of treatment).

The most common side effects of Afinitor is the development of mouth sores, infections due to neutropenia, rash, fatigue, diarrhea and decreased appetite. Rethink Breast Cancer had heard from a number of patients that they will endure these side effects in order to gain the benefits of prolonged quality of life.

The Canadian Breast Cancer Network interviewed one (1) patient with direct experience with everolimus for breast cancer. The patient indicated everolimus has helped her manage her disease and has allowed her to return to her daily routine working as a physician, which is extremely significant as this is the scenario that the patient is seeking.

The patient shared a little more in regards to her previous therapies since she was diagnosed with advanced breast cancer three years ago and the importance of multiple therapy options for advanced breast cancer when her previous treatment stopped working. The side effects of everolimus therapy did impact her quality of life, but due to the impact that it was having on stopping the progression of the disease, this patient indicated it was motivation enough to continue treatment. She also touched on the fact that because this is an oral drug it is easy to take as opposed to having to visit a hospital for the drug to be administered.

4.3 Additional Information

Both patient advocacy groups indicated that would like to have a better understanding of the weight that patient group submissions holds in the pCODR review process.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for everolimus (Afinitor) for advanced breast cancer. 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.pcodr.ca).

Overall Summary

Input on the everolimus (Afinitor) review was obtained from six of the nine of the provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, several enabling factors were identified for the use of everolimus in combination with exemestane. PAG noted that the limited population and ability to deliver treatment in the community setting as being favourable to implementation of a recommendation. PAG also identified several factors that may be set as barriers to implementation. PAG noted that issues around patient access to treatment may vary as oral cancer drug are funded differently than IV cancer treatment in some jurisdictions. PAG also noted that the retail pricing of everolimus may result in the potential doubling of treatment costs per patient in the event that a dose increase is required. PAG identified several areas where clarification would be helpful. These relate to the potential for dose adjustment and the duration of therapy for patients.

Please see below for more detailed PAG input on individual parameters.

5.1 Factors Related to Comparators

PAG noted that the main study under review evaluates the use of everolimus in combination with exemestane specifically and not other aromatase inhibitors.

As this is a pre-NOC submission the final indication is unclear. If the scope of the pCODR review is in combination with any non-steroidal aromatase inhibitor (NSAI) this could be potentially a large patient population. However, if the review is limited only to everolimus use in combination with exemestane, this may be a more limited patient population and an enabler to the implementation of a recommendation.

5.2 Factors Related to Patient Population

PAG noted that a combination therapy using everolimus exclusively with exemestane is favourable to funding as the patient population is limited. On the other hand the use of everolimus with all aromatase inhibitors would greatly increase the patient population and present a barrier to funding.

As above, as this is a pre-NOC submission, the scope of the review will require confirmation with the Clinical Guidance Panel.

5.3 Factors Related to Accessibility

As an oral agent, PAG identified everolimus as a treatment that can be delivered to patients easily in both rural and urban settings. As such, PAG identified the ease in accessibility of treatment for patients as an enabler.

PAG noted that everolimus is an oral medication, and in some jurisdictions, oral medications are not covered in the same way as intravenous cancer medications, which may limit accessibility. For these jurisdictions, patients 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. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenditure.

5.4 Factors Related to Dosing

PAG requested clarification regarding the need for dose adjustment of everolimus therapy in this patient population. PAG also noted that since aromatase inhibitors rarely have dose adjustments, monitoring this patient population for toxicity may be a new issue presenting a challenge to implementation.

5.5 Factors Related to Implementation Costs

In considering potential barriers to implementation PAG noted that, as a new treatment being added to an existing therapy, everolimus may add to the prescription workload. Another potential barrier involves the retail pricing of everolimus. PAG noted that since all doses of everolimus are priced the same, dose decreases for patients will require a combination of two doses (eg 2.5mg + 5mg to make 7.5mg) and is likely to increase the cost burden on a per patient basis. PAG requested clarity around the pricing of everolimus in comparison to other relevant treatments in this patient population of advanced breast cancer.

5.6 Other Factors

PAG requested clarity regarding the duration of therapy described. Drug information databases indicate that therapy is continued until no longer clinically beneficial or until unacceptable toxicity is observed in patients, which PAG identified as a potential barrier to implementation.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of everolimus on patient outcomes compared to standard therapies or placebo in the treatment of postmenopausal women with hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer that has progressed despite previous treatment with non-steroidal aromatase inhibitors (NSAIs) (see Table 1 in Section 6.2.1 for outcomes of interest and comparators).

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished double-blind RCT	Postmenopausal women with HR+ and HER2- advanced breast cancer that has progressed despite previous treatment with NSAIs Patients with HER2-overexpressing tumours or brain metastases are excluded.	Everolimus 10 mg/day (oral) in combination with exemestane	Placebo + a 2nd line endocrine therapy (exemestane, fulvestrant, tamoxifen) Steroidal and non-steroidal therapy	• OS • PFS • HRQoL • CBR • TTP • SAE • AE • WDAE

AE=adverse events; **CBR**=clinical benefit rate; **HER2-**=human epidermal growth factor receptor 2-negative; **HR+**= hormone receptor-positive; **HRQoL**=health-related quality of life; **NSAI**=non-steroidal aromatase inhibitor; **OS**=overall survival; **PFS**= progression-free survival; **RCT**=randomized controlled trial; **SAE**=serious adverse events; **TTP**=time to progression; **WDAE**=withdrawal due to adverse events

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

6.2.2 Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (2012, Issue 12) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Afinitor (everolimus) and breast cancer.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but not limited by publication year. The search is considered up to date as of February 6, 2013.

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 Ontario Institute for Cancer Research – Ontario Cancer Trials and Canadian Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium (SABCS) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

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

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

6.2.4 Quality Assessment

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

6.2.5 Data Analysis

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

6.2.6 Writing of the Review Report

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

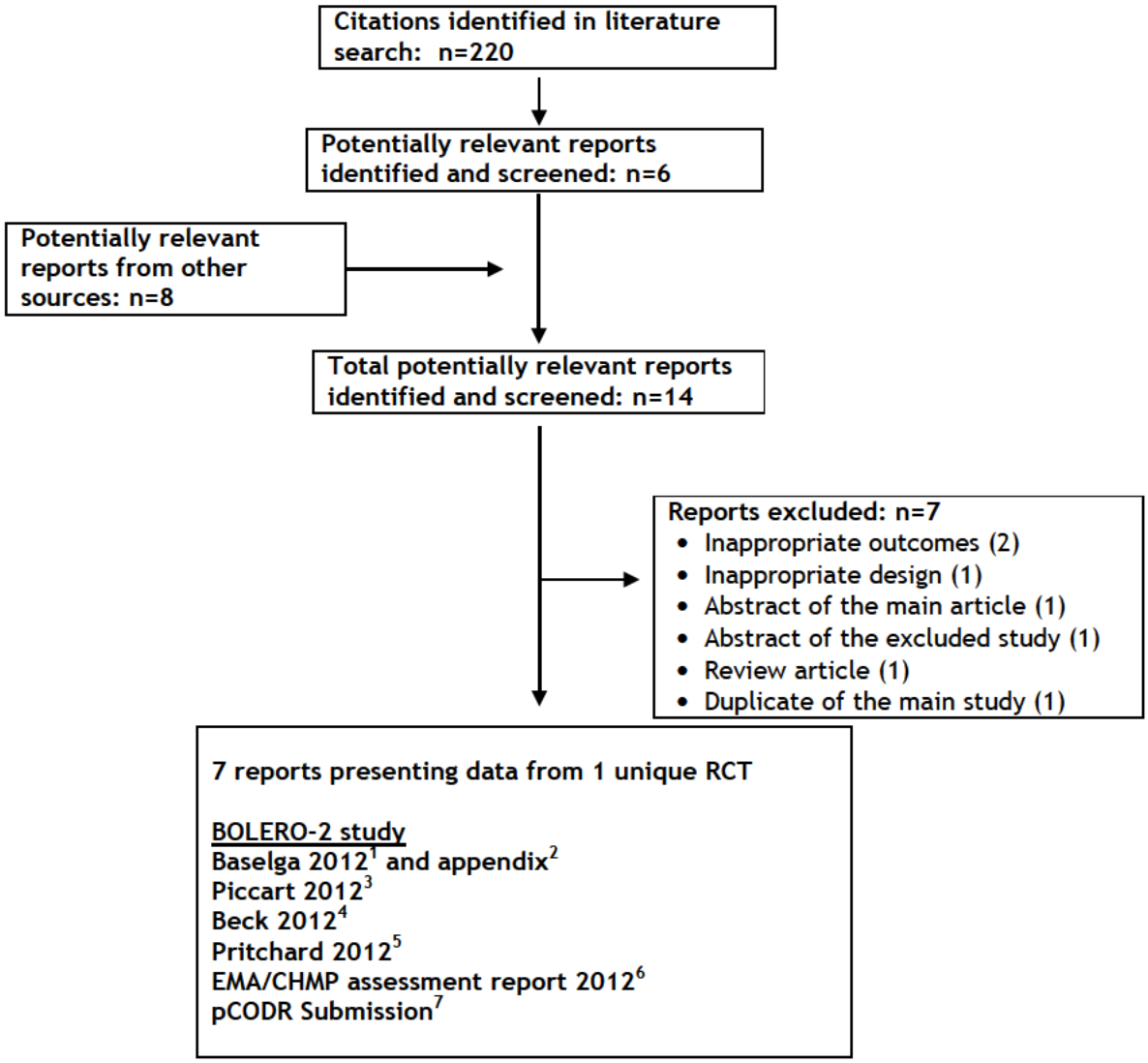
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions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

6.3 Results

6.3.1 Literature Search Results

Of the 14 potentially relevant reports identified, 7 studies were included in the pCODR systematic review[1-7] and 7 studies were excluded. Studies were excluded because they were duplicate of the main study,[20] abstract of the main study,[21] inappropriate outcomes,[22,23] review article,[24] abstract of an excluded study,[25] and inappropriate design.[26]

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 2: Summary of the BOLERO-2 study[1-7]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
International, double-blind, phase 3 study 196 centers, 24 countries (including Canada) Randomization period: Jun 2009 – Jan 2011 Randomization at 2:1 ratio was stratified on the basis of: • Visceral metastasis • Previous sensitivity to endocrine therapy Data cut-off for primary analysis: Feb 11, 2011 n=902 enrolled n=724 randomized n=724 analyzed	Postmenopausal women with ER+, HER2- advanced breast cancer, refractory to previous letrozole or anastrozole Have at least one measurable lesion or mainly lytic bone lesion Have an ECOG≤2 Exclusion: brain metastases, previous treatment with exemestane or mTOR inhibitors	Everolimus 10 mg oral daily (two 5-mg tablets) plus exemestane 25 mg oral daily Placebo plus exemestane 25 mg oral daily	Primary • Progression free survival Secondary • Overall survival • Clinical benefit rate • Time to deterioration of ECOG performance status • QoL (QLQ-C30, QLQ-BR23) • Safety • AEs, SAEs
AEs=adverse events; **ECOG**=Eastern Cooperative Oncology Group; **ER**=estrogen receptor; **HER2**=human epidermal growth factor receptor 2; **mTOR**=mammalian target of rapamycin; **SAEs**=serious adverse events			

a) Trials

One phase 3, double-blind, placebo-controlled RCT (The Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2)) was included in this review (see Table 2).[1-7] The purpose of this study was to evaluate the efficacy and safety of the combination of everolimus and exemestane in postmenopausal women with HR-positive breast cancer refractory to non-steroidal aromatase inhibitors. The study was conducted at 196 centers in 24 countries worldwide including Canada. It was sponsored by the manufacturer, who played a role in study design, data collection and data analysis.

Patients were randomized in a 2:1 ratio to receive treatment with either oral everolimus (10 mg daily) plus oral exemestane (25 mg daily) or placebo plus exemestane. Randomization was stratified by the presence of visceral metastasis, and by the documented sensitivity to prior hormonal therapy. The latter was defined as either at least 24 months of adjuvant hormonal therapy prior to recurrence, or a response or stabilization for at least 24 weeks of endocrine therapy for advanced disease.

According to the EMA assessment report,[6] patients were assigned to each treatment group by centralised allocation (i.e., interactive web response system [IWRS]/interactive voice

response system [IVRS]), in a double-blind manner. Full analysis set population consisted of all randomized patients (intention-to-treat, ITT). Safety analysis set population consisted of all patients who received at least one dose of study treatment and who had at least one valid post-baseline safety assessment. Three patients in the everolimus plus exemestane arm and one in the placebo plus exemestane arm did not receive study treatment.

A total of 528 progression free survival (PFS) events were required for the final analysis. A prespecified interim analysis was to be performed after observing 317 (60%) of the total PFS events. Patients were followed for survival after progression or study treatment discontinuation every 3 months until a total of 392 deaths was reached.

b) Populations

Of 902 patients enrolled in the study, 724 patients were randomly assigned to either the everolimus plus exemestane arm (n=485) or the placebo plus exemestane arm (n=239). Patient enrollment by region included Africa (6 patients), Asia Pacific (153 patients), Central and South America (5 patients), Europe-Middle East (286 patients) and North America (274 patients). Canada enrolled 51 patients or 7% overall. Randomization period was from June 2009 through January 2011. Overall, baseline characteristics were balanced between two treatment groups. The median age was 62 years for everolimus group (range 34-93) and 61 years for placebo group (range 28-90). Caucasians were predominant (74-78%) followed by Asians (19-20%). Overall, 56% of patients had visceral involvement, and 76-77% had bone metastasis. Thirty six percent had metastases in at least three organs. Most patients were of ECOG performance status of 0 (59-60%) and 1 (35-36%), only 2-3% of patients having ECOG performance status of 2. All patients had ER-positive and HER2-negative tumors, and 72% had progesterone-receptor-positive disease. Previous treatments included letrozole or anastrozole (100%), tamoxifen (47-49%), fulvestrant (16-17%), and chemotherapy (66-70%). Letrozole or anastrozole was the most recent therapy before randomization (74-75%). By protocol definition, 84% were sensitive to prior hormonal therapy.

c) Interventions

Patients received everolimus 10-mg daily (two 5-mg tablets)[6] or matching placebo in conjunction with exemestane 25 mg oral daily. Treatment continued until objective tumor progression was determined by radiologist (using Response Evaluation Criteria in Solid Tumors, RESIST 1.0), unacceptable toxicity, death, or discontinuation from the study for any other reason.[6] Patients with severe or intolerable adverse events may require dose reduction or interruption. Cross-over from placebo to everolimus was not allowed at the time of progression.[6] At the cut-off date (February 11, 2011) for interim primary analysis, 227 patients (47%) in the everolimus plus exemestane group and 69 patients (29%) in the placebo plus exemestane group still received study treatment. The median duration of exposure to everolimus was 14.6 weeks (range: 1 to 79) as compared with 12 weeks (range: 1 to 69) of exposure to placebo.[6] The median treatment duration of exemestane was 17.4 weeks (range: 1 to 79) in the combination therapy group and 12.0 weeks (range: 1 to 69) in the placebo.[6] Concomitant medications and other supportive care were not reported, except for baseline bisphosphonate use (44% for everolimus plus exemestane versus 55% for placebo plus exemestane).[23] According to the EMA report,[6] following discontinuation of study treatment, patients in both the combination arm and placebo arm were eligible to receive any post-treatment therapy (57.5% vs. 79.1%), including chemotherapy (33.4% vs. 54.4%), hormonal therapy (28.2% vs. 34.7%), radiotherapy (4.9% vs. 5.4%) and targeted therapy (2.7% vs. 7.5%).

d) Patient Disposition

Of the 902 screened for participation, 178 were excluded and 724 were randomized to two treatment groups at 2:1 ratio, which comprised the ITT population. The safety analysis population consisted of 720 patients received randomized therapy when four patients (three in the combination therapy and one in placebo) were excluded for not receiving allocated intervention. As of the data cut-off date for interim primary analysis at February 11, 2011, 296 patients were still on treatment, with 227 (47%) in the combination therapy group and 69 (29%) in the placebo group. As shown in Table 3, over half of the randomized populations discontinued the study treatment at the cut-off date, with more patients discontinued in the placebo group (53% vs. 71%). The main reason for discontinuation of treatment was disease progression (70% in combined therapy vs. 92.4% in placebo). Compared with placebo (exemestane alone), the combined therapy of everolimus plus exemestane had higher proportion of patients who discontinued treatment due to consent withdrawal (12.8% vs. 2.9%), adverse events (12.4% vs. 4.1%), death (2.7% vs. 0.6%) and protocol deviation (1.9% vs. 0). Follow-up of patients discontinued from treatment was not reported.

Table 3: Patient Disposition in the BOLERO-2 Study[1] (as of February 11, 2011)

	Everolimus and Exemestane	Placebo and Exemestane
Randomized, n	485	239
Received randomized therapy, n	482	238
Discontinued treatment, n (%)	258 (53.2)	170 (71.1)
• Disease progression, n (%)	181 (70.0)	157 (92.4)
• Consent withdrawal, n (%)	33 (12.8)	5 (2.9)
• Adverse events, n (%)	32 (12.4)	7 (4.1)
• Death, n (%)	7 (2.7)	1 (0.6)
• New therapy/protocol deviation, n (%)	5 (1.9)	0

Source: in Baselga et al. 2012, Figure 1 of Supplementary Appendix[2]

e) Limitations/Sources of Bias

BOLERO-2 was a phase 3 randomized double-blind placebo-controlled trial, in which patients and investigators who gave the treatment, assessed outcomes and conducted analyses were blinded to eliminate performance and assessor biases. Central randomization was carried out to ensure allocation concealment and balanced patient characteristics at baseline. The study was designed by academic investigators and by representatives of the sponsor, Novartis. Data were collected using the sponsor's data-management systems and were analyzed by sponsor's statistical team. The primary endpoint (PFS) was evaluated by local investigators and by independent committee. Results of PFS from both parties were agreeable. Cross-over from placebo to everolimus was not allowed at the time of progression. Other strengths of the study included an appropriate sample size and power calculation, ITT analysis, and subgroup and sensitivity analyses.

Potential limitations in the BOLERO-2 study include:

- PFS was the primary endpoint in this study. The statistically significant PFS benefit cannot be translated into survival benefit without survival data. This study reported the interim analyses for PFS, at which the OS results, a reliable and preferred health outcome in cancer research, were immature.

- Long-term risk-benefit of the drug, subsequent therapies after progression, and early discontinuation of treatment may affect the analysis of OS. Over half of randomized population discontinued the study treatment at the first interim PFS analysis, mostly due to disease progression followed by due to adverse events. Following progression, higher proportion of patients in the placebo arm received chemotherapy, hormonal therapy, radiotherapy and target therapy.
- Most patients included in this study were of ECOG performance status of 0 [59-60%] (patient is fully active) and 1 [35-36%] (patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light and sedentary nature); only 2-3% of patients having ECOG performance status of 2 (the patient is ambulatory and capable of all self-care but unable to work). The high proportion of patients with good performance status in this study raises concern about the generalizability of the findings for the indicated population. The effectiveness and safety of the study drug in patients with ECOG performance status ≥2 remain unknown.
- The high rates of adverse events specifically associated with the study drug such as stomatitis, rash, and pneumonitis may affect the integrity of blinding of investigators who provide treatment. Given that patients receiving study drug are more likely to be susceptible to inflammation events, appropriate measures might be taken to minimize those events that may influence the health outcomes and quality of life results.
- The HRQoL, as measured by the time to definitive deterioration for EORTC QLQ-C30 global health status, should be interpreted with caution, due to high drop-out rates in both groups and no post-progression/long-term QoL data.
- Generalizability is restricted by the rigorous selection criteria of the study; for instance, patients with history of brain metastasis, HER2-positive, and ECOG >2 were excluded.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The efficacy analysis on the basis of local and central assessment was conducted in the ITT population, which comprised of all randomized patients. The safety analysis was conducted in safety data set population, in which patients must receive at least one dose of study treatment and had at least one valid post-baseline safety assessment. The assessments of efficacy and safety were performed at baseline and every 6 weeks until disease progression. From the published article by Baselga et al. 2012,[1] the cut-off date for the interim primary analysis of progression-free survival (PFS) was February 11, 2011 (median follow-up 7.6 months), at which the overall survival results were still immature. The EMA report[6] presented three data cut-off updates for PFS: February 11, 2011 (median follow-up 7.6 months; July 08, 2011 (12.5 months); December 15, 2011 (17.7 months). The PFS results for cut-off date of December 15, 2011 were also presented in a conference abstract.[3] Tables 4 and 5 present the key outcomes from BOLERO-2 study for efficacy and safety, respectively.

Table 4: Summary of Key Trial Outcomes (Efficacy) from the BOLERO-2 Study (Everolimus plus exemestane, n=485; placebo plus exemestane, n=239)

PFS by local assessment	**Median (95% CI); months**	**HR (95% CI)**	**P-value**
Feb 11, 2011 (7.6 months)[a,b]	Everolimus: 6.9 (6.4, 8.1) Placebo: 2.8 (2.8, 4.1)	0.43 (0.35, 0.54)	<0.0001
Jul 08, 2011 (12.5 months)[a]	Everolimus: 7.4 (6.9, 8.5) Placebo: 3.2 (2.8, 4.1)	0.44 (0.36, 0.53)	<0.0001
Dec 15, 2011 (17.7 months)[a,c]	Everolimus: 7.8 (6.9, 8.5) Placebo: 3.2 (2.8, 4.1)	0.45 (0.38, 0.54)	<0.0001
PFS by central assessment[a]	**Median (months)**	**HR (95% CI)**	**P-value**
Feb 11, 2011 (7.6 months)[a,b]	Everolimus: 10.6 (9.5, NR) Placebo: 4.1 (2.8, 5.8)	0.36 (0.27, 0.47)	<0.0001
Jul 08, 2011 (12.5 months)[a]	Everolimus: 11.0 (9.6, NR) Placebo: 4.1 (2.8, 5.6)	0.36 (0.28, 0.45)	<0.0001
Dec 15, 2011 (17.7 months)[a,c]	Everolimus: 11.0 (9.7, 15.0) Placebo: 4.1 (2.9, 5.6)	0.38 (0.31, 0.48)	<0.0001
Overall survival	**Death, n (%)**	**HR (95% CI)**	**P-value**
Feb 11, 2011 (7.6 months)[b]	Everolimus: 52 (10.7) Placebo: 31 (13.0)	Not reported	
Second Interim OS analysis[a]	Everolimus: 112 (23.0) Placebo: 70 (29.3)	0.77 (0.57, 1.04)	0.046
		Median OS (95% CI)	
	Everolimus Placebo	NR (NR, NR) NR (20.7, NR)	
Dec 15, 2011 (17.7 months)[c]	Everolimus: 123 (25.4) Placebo: 77 (32.2)	Not reported	
Quality of Life[d]			
EORTC QLQ-C30	**Baseline GHS**	**Difference (95% CI)**	
	Everolimus: 64.7 Placebo: 65.3	-0.7 (-4.3, 3.0)	
Time to definitive deterioration	**MID = 5% change from baseline**	**Median TTD, months (95% CI)**	**P-value**
	Everolimus: n=254 (52%) Placebo: n=113 (47%)	8.3 (7.0, 9.7) 5.8 (4.2, 7.2)	0.0084
	MID = 10-point change from baseline		
	Everolimus: n=202 (42%) Placebo: n=84 (35%)	11.7 (9.7, 13.3) 8.4 (6.6, 12.5)	0.1017
Clinical benefit rate[e]	**n (%)**	**(95% CI)**	
Per investigator[a]	Everolimus: 162 (33.4) Placebo: 43 (18.0)	(29.2, 37.8) (13.3, 23.5)	<0.0001
Per central radiology review[a]	Everolimus: 150 (30.9) Placebo: 36 (15.1)	(26.8, 35.3) (10.8, 20.2)	not reported

CI=confidence interval; **CR**=complete response; **EORTC QLQ**=The European Organization for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire; **GHS**=Global Health Scale; **HR**=hazard ratio; **MID**=minimal important difference; **PFS**=progression free survival; **NR**=not reached; **SD**=stable disease; **TTD**=time to definitive deterioration

[a]Source: EMA report[6]
[b]Source: Baselga et al. 2012[1]
[c]Source: Piccart et al. 2012[3]
[d]Source: Beck et al. 2012,[4] cut-off date Dec 15, 2011
[e]Clinical benefit rate = proportion of patients with CR or PR or SD ≥ 24 weeks

Table 5: Summary of Key Trial Outcomes (Safety) from the BOLERO-2 Study*

Category[a]	Everolimus plus exemestane (n=482) n (%)	Placebo plus exemestane (n=238) n (%)
All deaths	**51 (10.6)**	**31 (13.0)**
On-treatment deaths[b]	12 (2.5)	4 (1.7)
SAEs	**110 (22.8)**	**29 (12.2)**
Suspected to be drug-related	52 (10.8)	3 (1.3)
AEs leading to discontinuation	**92 (19.1)**	**11 (4.6)**
Suspected to be drug-related	79 (16.4)	7 (2.9)
Any AEs	**481 (99.8)**	**210 (88.2)**
AEs suspected to be drug-related[c]	462 (95.9)	142 (59.7)
Grade 3-4 AEs	211 (43.8)	61 (25.6)
Other significant AEs	**450 (93.4)**	**161 (67.6)**
AEs leading to dose interruption and/or reduction	278 (57.7)	29 (12.2)
AEs=adverse events; **SAEs**=serious adverse events		

*Cut-off date February 11, 2011
[a]Source: EMA report[6]
[b]On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment
[c]Related to either one of the two drugs

Efficacy Outcomes

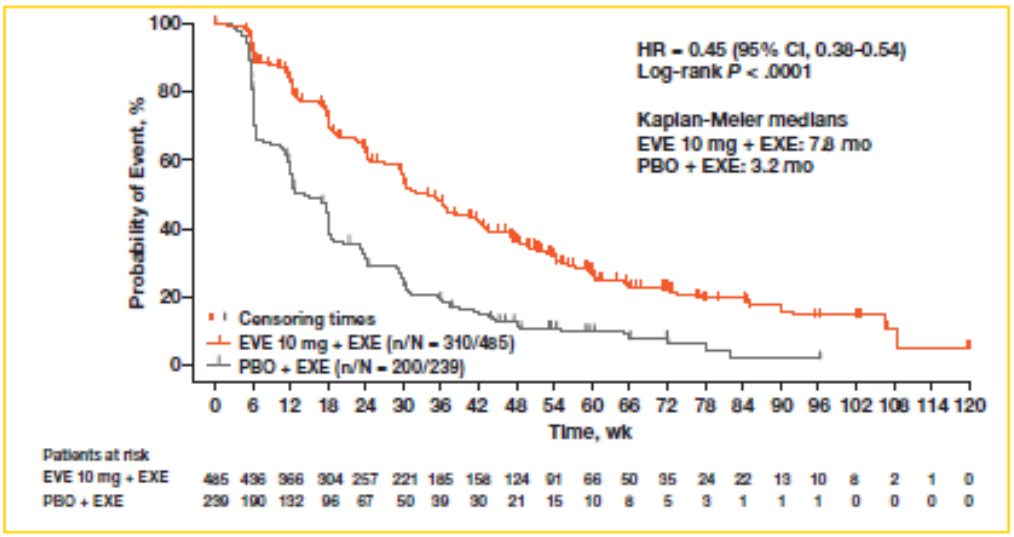
a) Overall Survival

Overall survival (OS) was the secondary endpoint in the BOLERO-2 study. It was defined as the time from the date of randomization to the date of death due to any cause. Kaplan-Meier methods were used to estimate the distribution function of OS. A stratified log-rank test at an overall one-sided 2.5% level of significance was performed to compare differences in OS between the two treatment groups. OS was evaluated only if PFS showed significant difference between treatment groups. Three OS analyses were planned: at the time of the interim analysis for PFS, after 173 deaths, and after 392 deaths.[6] The date of the interim analysis for PFS was February 11, 2011 (7.6 months).

The published article by Baselga et al. 2012[1] reported that the OS results were immature at the interim analysis for PFS. At that time, there were a total of 83 deaths: 52 (10.7%) in the everolimus group; 31 (13.0%) in the placebo group. The EMA report[6] showed results of the second interim analysis, where 182 deaths were observed: 112 (23%) in the everolimus group; 70 (29%) in the placebo group. The median OS and its 95% confidence interval have not been reached for each treatment group. The recent update results of BOLERO-2 at cut-off date for final PFS analysis (December 15, 2011; 17.7 months), showed that there were a total of 200 deaths, of which 25.4% (n=123) in the everolimus group and 32.3% (n=77) in the placebo group.[3]

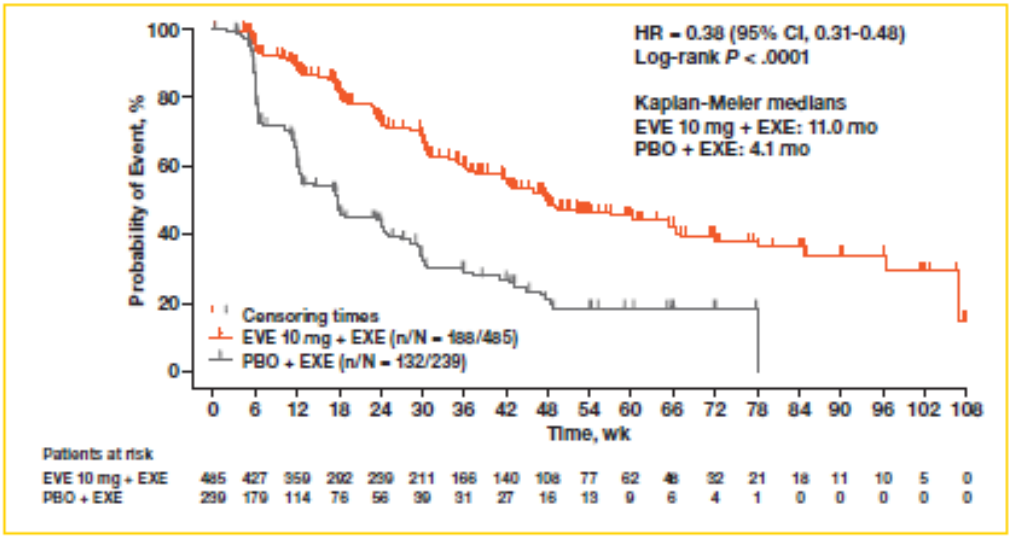
b) Progression Free Survival

A. PFS local assessment



Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo.

B. PFS central assessment



Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo.

Figure 1: Kaplan-Meier Plot of Progression Free Survival (data cut-off December 15, 2011; from Piccart et al. 2012[3]

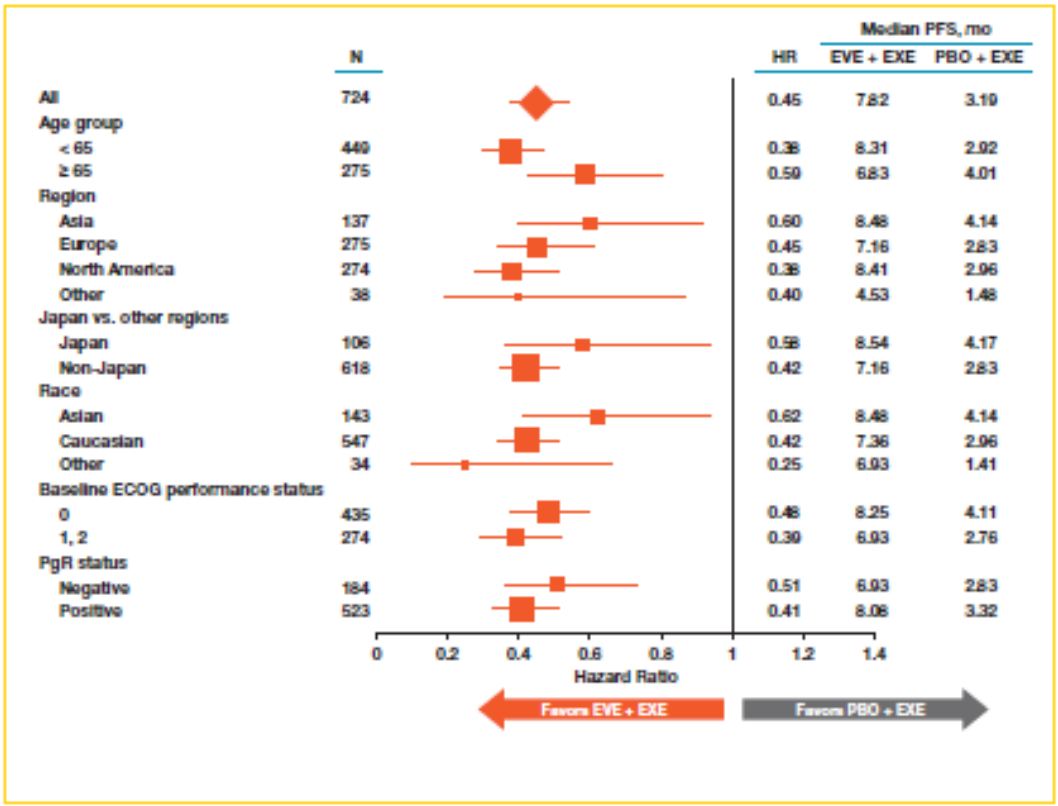
The primary endpoint in the BOLERO-2 study was PFS, which was defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. Kaplan-Meier methodology was used to estimate the PFS distribution for each treatment group. A stratified log-rank test was performed to assess differences in PFS between treatment groups. The study was designed to provide 90% power at 2.5% level of significance to detect a hazard ratio of 0.74, with a total 528 PFS events required for the final analysis. An interim analysis was performed after observing approximately 60% of the

total PFS events (actual event count was 359). The published article by Baselga et al. 2012[1] reported results of the interim PFS analysis based on February 11, 2011 cut-off (median follow-up 7.6 months). The EMA report[6] showed three data cut-off updates for PFS: 1st interim PFS analysis by February 11, 2011 (7.6 months), 2nd interim PFS analysis by July 08, 2011 (12.5 months), and final PFS analysis by December 15, 2011 (17.7 months). A conference abstract by Piccart et al. 2012[3] reported the results of PFS analysis on December 15, 2011.

As of December 15, 2011 data cut-off for final PFS analysis, there were a total of 510 events (progression or death from any cause) on the basis of local investigator assessment: 310 (63.9%) for everolimus plus exemestane versus 200 (83.7%) in the placebo plus exemestane. There were a total 320 events on the basis of central radiology assessment: 188 (38.8%) for everolimus plus exemestane versus 132 (55.2%) for placebo plus exemestane. The median PFS on the basis of investigator assessment was 7.8 months for everolimus plus exemestane versus 3.2 months for placebo plus exemestane (HR 0.45; 95% CI 0.38, 0.54; P<0.0001). The median PFS on the basis of central assessment was 11.0 months versus 4.1 months, respectively (HR 0.38; 95% CI 0.31, 0.48; P<0.0001). The results for the first and second PFS interim analysis were showed in Table 4. Kaplan-Meier plots of progression free survival for data cut-off February 11, 2011 are shown in Figure 1.

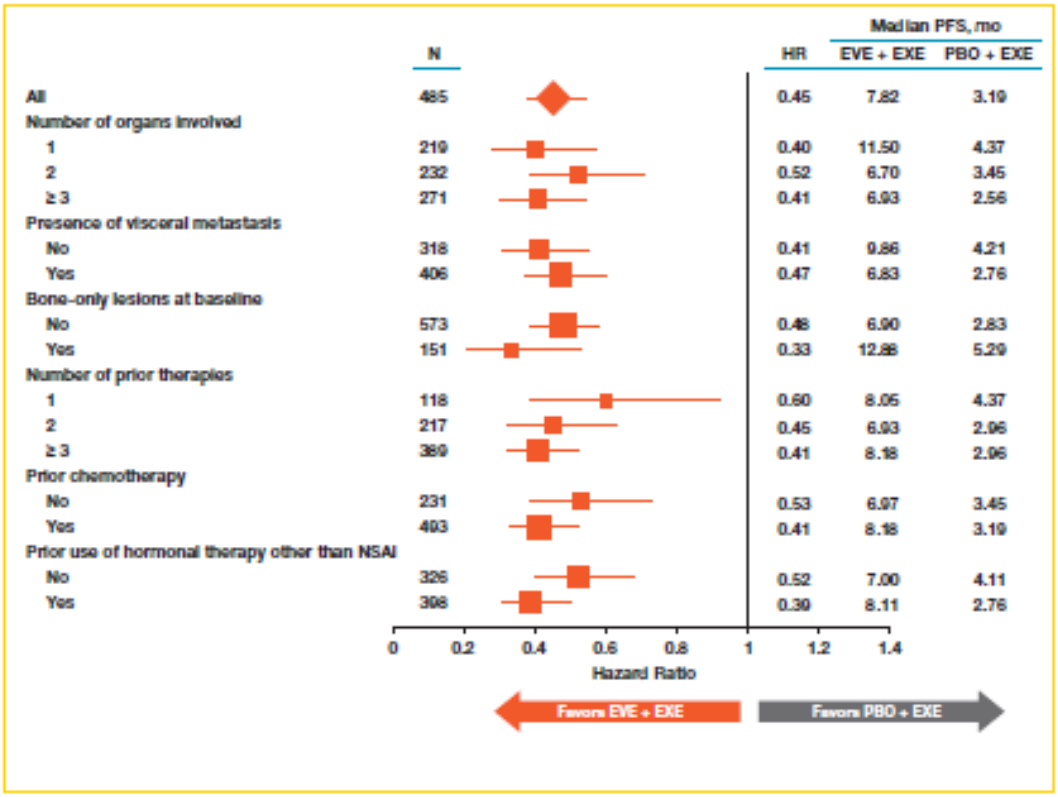
The results for PFS were consistent in all subgroups (Figure 2, A and B).[1]

A. By patient characteristics and hormone receptor status



Abbreviations: ECOG, Eastern Cooperative Oncology Group; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival; PgR, progesterone receptor.

B. By extent of disease and prior therapy



Abbreviations: EVE, everolimus; EXE, exemestane; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; PBO, placebo; PFS, progression-free survival.

Figure 2: Results for PFS across various subgroups (cut-off date December 15, 2011; from Piccart et al. 2012[3]

C) Health-Related Quality of Life

The health-related quality of life (HRQoL) was a secondary outcome in the BOLERO-2 study and the scores were analyzed over time using the European Organization for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and its breast cancer-specific complementary measure (EORTC QLQ-BR23) questionnaires.[4] The QLQ-C30 consists of 30 items combined into 15 subscales including a Global Health Status (GHS) subscale; total scores range from 0 to 100, with higher scores indicate better HRQoL. The accepted minimal important difference (MID) values for different subscales of the EORTC QLQ-C30 range from 5% to 10%.[27-29] In BOLERO-2, time to definitive deterioration (TTD) (at a 5% decrease in score relative to baseline without subsequent increase above this threshold, or 10 points reduction from baseline) was used to assess the change in HRQoL. The data were evaluated at baseline and every 6 weeks thereafter until disease progression.

At baseline, the EORTC QLQ-C30 GHS scores were similar between treatment groups (64.7 for everolimus plus exemestane versus 65.5 for placebo plus exemestane; difference -0.7 [95% CI -4.3, 3.0]). At the cut-off date of December 15, 2011, the median TTD in HRQoL was 8.3 months (95% CI 7.0, 9.7) for everolimus plus exemestane versus 5.8 months (95% CI 4.2, 7.2) for placebo plus exemestane (P=0.0084) when MID was set at 5% change from baseline. The hazard ratio corresponding with MID at 5% was 0.74 (95% CI 0.58, 0.95). However, the difference in median TTD between treatments was not statistically significant when MID was set at 10 points: 11.7 months (95% CI 9.7, 13.3) versus 8.4 months

(95% CI 6.6, 12.5), respectively; P=0.1017. The hazard ratio was 0.80 (95% CI 0.61, 1.06) based on MID of 10. There was no statistically significant difference in EORTC QLQ GHS between treatment groups for any defined subgroups, based on the MID 5% or MID 10.[4]

d) Clinical Benefit Rate

The clinical benefit rate (CBR) was defined as the proportion of patients with complete response (CP) or partial response (PR) or stable disease (SD) with at least 24 weeks. By investigator assessment, the CBRs (95% CI) were 33.4% (29.2, 37.8) and 18.0% (13.3, 23.5) in the everolimus plus exemestane and placebo plus exmestane arms, respectively. By central assessment, the CBRs (95% CI) were 30.9% (26.8, 35.3) and 15.1% (10.8, 20.2), respectively.

Harms Outcomes

The safety analysis population consisted of 720 patients, 482 in everolimus plus exemestane and 238 in placebo. Four patients in the ITT population did not receive allocated intervention, and were therefore excluded from the safety analysis set. Adverse events were monitored continuously throughout the study and graded using the National Cancer Institute Common Terminology Criteria for Adverse events (NCI-CTCAE), version 3.0.

As of February 11, 2011, the median duration of exposure to everolimus was 14.6 weeks (range: 1 to 79); the median duration of exposure to exemestane in the everolimus arm was 17.4 weeks (range 1 to 79); the median durations of the placebo and exemestane in the control arm were both 12.0 weeks (range 1 to 69). Results of harm outcomes are shown in Table 5.

a) Death

Fifty-one patients (10.6%) in the everolimus plus exemestane and 31 patients (13.0%) in the placebo plus exemestane died as of the interim date for PFS analysis (February 11, 2011). Of those, 12 patients (2.5%) in the everolimus plus exemestane and 4 patients (1.7%) in the placebo plus exemestane died on-treatment. Seven (1.5%) deaths due to SAEs occurred in the everolimus plus exemestane versus one (0.4%) in the placebo plus exemestane.[6]

b) Serious Adverse Events

Reported serious adverse events (SAEs) were more common in the everolimus plus exemestane group (n=110, 22.8%) compared with the placebo plus exemestane group (n=29, 12.2%). The most common SAEs in the everolimus plus exemestane group were pneumonitis (2.5%), pneumonia (1.5%), anemia, dyspnea, pulmonary embolism, pyrexia, and renal failure (all in 1.2%).[6]

There were 10.8% in the everolimus plus exemestane (n=52) and 1.3% in the placebo plus exemestane (n=3) that were suspected to be drug-related. The most common drug-related serious adverse events were pneumonitis (12 [2.5%] in everolimus; 0 in placebo), renal failure (5 [1.0%]; 0) and hyperglycemia (4 [0.8%]; 0).[6]

c) Adverse Events Leading to Discontinuation

There were more AEs leading to discontinuation of therapy in the everolimus plus exemestane group (n=92, 19.1%) compared with the placebo plus exemestane group (n=11, 4.6%). Of those, 16.4% in the everolimus plus exemestane and 2.9% in the placebo plus exemestane were suspected to be drug related. The most common adverse events leading to discontinuation were pneumonitis (3.9%), stomatitis (2.3%), fatigue (1.9%), decreased appetite (1.7%), dyspnea (1.7%), anemia (1.2%), and nausea (1.0%).[6]

d) Any Adverse Events

More patients in the everolimus plus exemestane group experienced at least one adverse event than those in the placebo plus exemestane group (481, 99.8% versus 210, 88.2%).[6] Of those, 95.9% in the everolimus plus exemestane (n=462) and 59.7% in the placebo plus exemestane (n=142) were suspected to be drug related. Adverse events and grading with suspected relationship to study drug are shown in Table 6. The most common drug related adverse events, with incidence ≥10% in the everolimus plus exemestane group were stomatitis (55.8% vs. 10.5% placebo), rash (32.2% vs. 4.6%), fatigue (21.6% vs. 16.4%), decreased appetite (19.3% vs. 5.5%), diarrhea (18.3% vs. 8.8%), dysgeusia (18.0% vs. 3.8%), nausea (17.0 vs. 15.1%), pneumonitis (12.4% vs. 0%), weight loss (10.8% vs. 2.1%), epistasis (10.0% vs. 0.4%), and thrombocytopenia (10.0% vs. 0%).

Table 6: Adverse Events and Grading with Suspected Relationship to Study Drug

	Everolimus plus exemestane N=482			Placebo plus exemestane N=238		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Any preferred term	**462 (95.9)**	**149 (30.9)**	**15 (3.1)**	**142 (59.7)**	**16 (6.7)**	**2 (0.8)**
Stomatitis	269 (55.8)	37 (7.7)	0	25 (10.5)	2 (0.8)	0
Rash	155 (32.2)	4 (0.8)	0	11 (4.6)	0	0
Fatigue	104 (21.6)	10 (2.1)	2 (0.4)	39 (16.4)	0	0
Decreased appetite	93 (19.3)	3 (0.6)	0	13 (5.5)	0	0
Diarrhoea	88 (18.3)	6 (1.2)	1 (0.2)	21 (8.8)	1 (0.4)	0
Dysgeusia	87 (18.0)	1 (0.2)	0	9 (3.8)	0	0
Nausea	82 (17.0)	1 (0.2)	1 (0.2)	36 (15.1)	0	0
Pneumonitis	60 (12.4)	15 (3.1)	0	0	0	0
Weight decreased	52 (10.8)	2 (0.4)	0	5 (2.1)	0	0
Epistaxis	48 (10.0)	0	0	1 (0.4)	0	0
Thrombocytopenia	48 (10.0)	10 (2.1)	1 (0.2)	0	0	0
Hyperglycaemia	45 (9.3)	16 (3.3)	1 (0.2)	4 (1.7)	1 (0.4)	0
Headache	43 (8.9)	0	0	13 (5.5)	0	0
Pruritus	43 (8.9)	1 (0.2)	0	5 (2.1)	0	0
Alanine aminotransferase increased	42 (8.7)	12 (2.5)	0	6 (2.5)	3 (1.3)	0
Anaemia	42 (8.7)	10 (2.1)	2 (0.4)	4 (1.7)	1 (0.4)	0
Aspartate aminotransferase increased	40 (8.3)	11 (2.3)	0	10 (4.2)	1 (0.4)	0
Dyspnoea	40 (8.3)	11 (2.3)	0	6 (2.5)	0	0
Cough	39 (8.1)	2 (0.4)	0	7 (2.9)	0	0
Asthenia	32 (6.6)	5 (1.0)	0	1 (0.4)	0	0
Hypercholesterolaemia	32 (6.6)	1 (0.2)	0	2 (0.8)	0	0
Vomiting	31 (6.4)	1 (0.2)	1 (0.2)	10 (4.2)	0	0
Neutropenia	30 (6.2)	11 (2.3)	0	0	0	0
Dry mouth	29 (6.0)	0	0	8 (3.4)	0	0
Nail disorder	28 (5.8)	0	0	1 (0.4)	0	0
Alopecia	26 (5.4)	0	0	8 (3.4)	0	0
Constipation	26 (5.4)	0	0	10 (4.2)	0	0
Oedema peripheral	26 (5.4)	3 (0.6)	0	4 (1.7)	0	0
Dry skin	24 (5.0)	0	0	2 (0.8)	0	0
Arthralgia	23 (4.8)	1 (0.2)	0	15 (6.3)	0	0
Hot flush	11 (2.3)	0	0	25 (10.5)	0	0

Source: The EMA Assessment Report 2012[6]

e) Adverse Events Requiring Dose Interruption and/or Reduction

More patients in the everolimus plus exemestane group experienced AEs that required dose interruption/reduction than those in the placebo plus exemestane group (278, 57.7% versus 29, 12.2%).[6] The most common AEs leading to dose interruption/reduction in the everolimus plus exemestane group were stomatitis (22.0%), pneumonitis (6.0%), and thrombocytopenia (5.0%).[6]

6.4 Ongoing Trials

The European Medicines Agency/Committee for Medicinal Products for Human Use (EMA/CHMP)[6] required the manufacturer to submit the results of the BOLERO-6 study as the condition of the marketing authorisation. It is a three-arm, randomized, open label, phase II study of everolimus in combination with exemestane versus everolimus alone versus capecitabine in the treatment of postmenopausal women with oestrogen receptor-positive, locally advanced, recurrent, or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole. Due date for the submission of Clinical Study Report of BOLERO-6 to EMA/CHMP is by 3rd quarter of 2017.

At present, one related on-going trial was identified.[30]

Status	Study
Active	Title: A Phase IIIB, Multi-Center, Open Label Study For Postmenopausal Women With ER+ Locally Advanced or Metastatic Breast Cancer Treated With Everolimus (RAD001) in Combination With Exemestane: 4EVER - Efficacy, Safety, Health Economics, Translational Research Study ID: NCT01626222; CRAD001JDE49 Design: multi-center, open-label, single-arm N= 300, estimated Primary Objective: evaluate the efficacy, safety, quality of life and health resources utilization in postmenopausal women with HR+ breast cancer progressing following prior therapy with non-steroidal AIs treated with the combination of Everolimus and Exemestane Treatment arms: everolimus in combination with exemestane Primary outcome: ORR after 24 weeks of treatment Secondary outcomes: PFS after 48 weeks; ORR after 48 weeks; OS after 48 weeks; safety within 48 weeks; resource utilization ; HRQoL (EORTC QLQ-30, BR23, EQ-5D) Duration: 48 weeks Start date: June 2012 End date: May 2014

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

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

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

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

The Breast Clinical Guidance Panel is comprised of three 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 pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Embase 1974-present (oemezd) Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily and Ovid MEDLINE (R) (pmez)

#	Searches	Results
1	(everolimus* or Afinitor* or Affinitor* or "RAD 001" or RAD001 or rad001a or rad 001a or SDZ-RAD or SDZRAD or certican* or Zortress* or 159351-69-6 or Votubia*).ti,ab,ot,sh,hw,rn,nm.	11795
2	exp Breast Neoplasms/ or exp carcinoma, intraductal, noninfiltrating/ or exp Phyllodes Tumor/	527676
3	(((breast or breasts or mammary or nipple*) adj3 (cancer* or neoplasm* or tumour* or tumor* or cancer or cancers or cancerous or carcinoma* or adenocarcinoma* or carcinoid or carcinoids or leukemia or lymphoma* or cyst or neuroblastoma* or metastases or metastasis or metastatic or malignan* or sarcoma* or oncolog* or carcinogenes* or fibroadenoma*)) or paget disease* or paget nipple* or cystosarcoma phylloide*).ti,ab.	493967
4	or/2-3	630195
5	1 and 4	1214
6	5 use pmez	112
7	(everolimus* or Afinitor* or Affinitor* or "RAD 001" or RAD001 or rad001a or rad 001a or SDZ-RAD or SDZRAD or certican* or Zortress* or 159351-69-6 or Votubia*).ti,ab.	6262
8	*Everolimus/	2533
9	or/7-8	6481
10	exp *breast tumor/	399999

11	(((breast or breasts or mammary or nipple*) adj3 (cancer* or neoplasm* or tumour* or tumor* or cancer or cancers or cancerous or carcinoma* or adenocarcinoma* or carcinoid or carcinoids or leukemia or lymphoma* or cyst or neuroblastoma* or metastases or metastasis or metastatic or malignan* or sarcoma* or oncolog* or carcinogenes* or fibroadenoma*)) or paget disease* or paget nipple* or cystosarcoma phylloide*).ti,ab.	493967
12	or/10-11	557667
13	9 and 12	311
14	13 use oemezd	213
15	or/6,14	325
16	limit 15 to english language	305
17	remove duplicates from 16	213

2. Literature search via PubMed
Search History

Search	Add to builder	Query	Items found
#3	Add	Search #1 AND #2	7
#2	Add	Search publisher[sb]	421039
#1	Add	Search (everolimus* OR Afinitor* OR Affinitor* OR "RAD 001" OR RAD001 OR rad001a OR rad 001a OR SDZ-RAD OR SDZRAD OR certican* OR Zortress* OR 159351-69-6[rn] OR everolimus[Supplementary Concept] OR Votubia*) AND ("Breast Neoplasms"[Mesh] OR "Carcinoma, Intraductal, Noninfiltrating"[Mesh] OR ("Phyllodes Tumor"[Mesh]) OR ((breast[tiab] OR breasts[tiab] OR mammary[tiab] OR nipple*) AND (cancer*[tiab] OR neoplasm*[tiab] OR tumour*[tiab] OR tumor*[tiab] OR cancer[tiab] OR cancers[tiab] OR cancerous[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR carcinoid[tiab] OR carcinoids[tiab] OR leukemia[tiab] OR lymphoma[tiab] OR cyst[tiab] OR metastases[tiab] OR neuroblastoma*[tiab] OR metastasis[tiab] OR metastatic[tiab] OR malignan*[tiab])))	112

3. Cochrane Central Register of Controlled Trials (Central)

Cochrane Central Register of Controlled Trials : Issue 12 of 12, December 2012

Description:

#1 everolimus* or Afinitor* or Affinitor* or RAD 001 or RAD001 or rad001a or rad 001a or SDZ-RAD or SDZRAD or certican* or Zortress* or 159351-69-6 or Votubia*:ti,ab,kw in Trials (Word variations have been searched) [336]

#2 ((breast or breasts or mammary or nipple*) and (cancer* or neoplasm* or tumour* or tumor* or cancer or cancers or cancerous or carcinoma* or adenocarcinoma* or carcinoid or carcinoids or leukemia or lymphoma or cyst or neuroblastoma* or metastases or metastasis or metastatic or malignan*)) [15709]

#3 MeSH descriptor: [Breast Neoplasms] explode all trees [7509]

#4 MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees [78]

#5 MeSH descriptor: [Phyllodes Tumor] explode all trees [1]

#6 #2 or #3 or #4 or #5 [15714]

#7 #1 and #6 [9]

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
http://www.ontario.canadiancancertrials.ca/

Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search terms: (Afinitor OR everolimus) AND (breast cancer)

Select international agencies including:

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

European Medicines Agency (EMA):
http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp

Search terms: (Afinitor OR everolimus) AND (breast cancer)

Conference abstracts:

American Society of Clinical Oncology (ASCO)

http://www.asco.org/

San Antonio Breast Cancer Symposium (SABSC)
http://www.sabcs.org/

Search terms: (Afinitor OR everolimus) AND (breast) / last 5 years

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