Application for changes to the Pharmaceutical Schedule

A guide to help people, clinicians, clinical groups and consumer groups prepare funding applications to PHARMAC

Foreword

PHARMAC is the government agency that decides, on the behalf of District Health Boards, which pharmaceuticals should be publicly fund in New Zealand. For more information on the process PHARMAC uses to make its funding decisions and how we determine if a proposal to fund a treatment would help us achieve our Statutory Objective, please visit the PHARMAC website.

PHARMAC's objective is "to secure, for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided".

Each year, PHARMAC receives a large number of applications that contain proposals either to fund new pharmaceuticals or to widen access to pharmaceuticals that we already fund. As PHARMAC must work within a fixed budget, we need to make difficult choices about which applications we should progress to a funding decision at any given time. This involves assessing large amounts of often complex information, to identify those proposals that would provide the best health outcomes.

We have written this funding application form for people, clinicians, clinical groups and consumer groups to use. We recognise that some individuals and groups won't have the same resource as pharmaceutical suppliers to prepare applications. This form is to help you provide the right information in order to progress the application.

This form is a guide – you don't have to follow it in detail, or at all, but it will make processing your application much easier and may reduce the time involved. If you don't know some information, please feel free to leave those sections blank; however the form does outline the general information that we need to assess a funding application. Having your application address these points may reduce follow-up questions to you, and could speed up how quickly we consider it.

The *Guidelines for Funding Applications to PHARMAC*, updated in 2015, set out the full information that we need to progress any funding application. We expect pharmaceutical suppliers to follow the full *Guidelines for Funding Applications to PHARMAC* when submitting a funding application. However, as an applicant, please feel free to view them should you wish to have more detailed information on submitting an application.

Send your applications to us at:

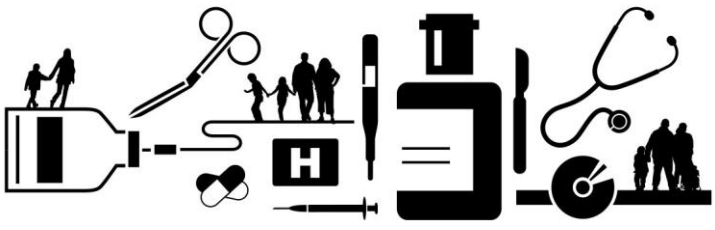
Email: **applications@pharmac.govt.nz**
Post: **PO Box 10254**
The Terrace
Wellington 6143

You may also find it beneficial to talk to the relevant Therapeutic Group Manager at PHARMAC before you make a formal funding application. Please email us as above, and we will contact you.

We will keep you informed of progress. We publish and regularly update a record of all current funding applications via the Application Tracker on our website (**www.pharmac.govt.nz**), which details the current status of applications and relevant PTAC and subcommittee minutes.

Please note:

- We need you to supply copies of referenced articles that support the application, wherever possible. Have them referenced in the relevant section of the application form, and clearly say which (if any) cited publications you cannot provide.
- We prefer funding applications related to medicines that have been registered by Medsafe. While we can consider funding applications for unregistered medicines or unregistered indications, this is determined on a case–by-case basis.
- We may decide to defer our assessment of your application until we receive a full funding application from the supplier, which they would need to prepare in accordance with the full *Guidelines*.



PHARMAC
Pharmaceutical Management Agency

New Zealand Government

Changes to the Pharmaceutical Schedule Application

Applicant

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Department & DHB, practice or organisation
Breast Cancer Aotearoa Coalition

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Phone or pager
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Are you making this application on behalf of a wider group (department, society, special interest group)? If so, who?
Breast Cancer Aotearoa Coalition

Is there anyone else that we should contact if we have questions about specific parts of this application?
No

Proposed pharmaceutical

Chemical
everolimus

Presentations and strengths
Tablets 2.5mg, 5mg and 10mg

Brand name(s)
AFINITOR®

Suppliers (eg pharmaceutical companies, wholesalers)
Novartis

Price
The current prices listed in the Pharmaceutical Schedule are $6512.29 for 30x10mg and $4555.76 for 30x5mg tablets.

Is it registered by Medsafe?
Registered for other indications but not for breast cancer

Describe the indication(s) that funding is being sought for.
Treatment of women with hormone receptor positive HER-2 negative advanced breast cancer (ABC) – in combination with exemestane (or tamoxifen or fulvestrant) in post-menopausal women after recurrence or progression following a non-steroidal aromatase inhibitor.

If this pharmaceutical has been registered by Medsafe, is it licenced for these indications? If not, is it licenced for these indications overseas? Please provide details.

No registration for breast cancer in New Zealand. Details of current overseas approvals are as follows:
European Union (EMEA)
Indicated for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in post-menopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor. (This indication was approved in 2012). (1)
USA (FDA)
Indicated for post-menopausal women with advanced hormone receptor-positive, HER2 negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole. (This indication was approved in 2012)
Australia (TGA)
Indicated for treatment of post-menopausal women with hormone receptor-positive, HER2 negative advanced breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole (2).

How many people in New Zealand do you expect would receive the pharmaceutical?

The number of people who would receive the pharmaceutical annually is dependent on restrictions that might be recommended for access to treatment. ER (oestrogen receptor) positive breast cancer is the most common variant and responsible for most deaths – however treatment with everolimus would only extend to patients who had developed resistance to existing therapy and who are suitable for everolimus treatment (or who are not suitable for existing funded treatments).

What is the expected dosing?

The recommended dose is 10 mg to be taken once daily (2). Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. Management of severe and/or intolerable suspected adverse reactions may require dose reduction and/or temporary interruption of therapy. For adverse reactions of Grade 1, dose adjustment is usually not required. If dose reduction is required, the recommended dose is 5 mg daily and must not be lower than 5 mg daily.

What is the likely duration of treatment, if patients respond to treatment?

A US study that compared time on treatment (TOT) among patients treated with everolimus and chemotherapy found that, in 940 everolimus patients, the median TOT ranged from 5.5 to 7.2 months (3). However this is highly dependent on stage of disease. In BOLERO-2 the median PFS (progression free survival) (final analysis) in the everolimus/exemestane treated group was 7.8 months for investigator review and 11 months for central review (4). In reported observational studies, the duration of therapy ranged between 3-12 months.

Describe the setting that this pharmaceutical would be used in. Is the need for this this treatment limited to a hospital setting, or is it also required in the community? If in hospital, is it theatre only, on medical wards, or in outpatient clinics?

This treatment can be administered to outpatients in the community setting.

If this is a new pharmaceutical, are there likely to be other uses for it?

This is not a new pharmaceutical – it already has other uses (5).

Treatment initiation

Is treatment with the pharmaceutical started empirically? If so, please describe the symptoms, signs or other features necessary to initiate therapy.

Diagnosis of advanced breast cancer with hormone receptor positivity and failure of treatment with aromatase inhibitor alone (as evidenced by disease advancement).

Are there any specific tests needed to confirm diagnosis? If so, please name these tests, and say whether these are currently performed routinely, where they take place, and whether they are funded.

Clinical examination, Imaging and Pathology – not specific to this treatment but would be monitored for ABC patients.

Should other therapies have been used prior to starting treatment with this pharmaceutical? If so, which?

ASCO Guidelines (2016) state that sequential hormone therapy is the preferential treatment for most women with HR-positive MBC (metastatic breast cancer). Treatment recommendations should be based on type of adjuvant treatment, disease-free interval, and organ function. For post-menopausal women, aromatase inhibitors (AIs) are the preferred first-line endocrine therapy, with or without the cyclin-dependent kinase inhibitor palbociclib. As second-line therapy, fulvestrant should be administered at 500 mg with a loading schedule and may be administered with palbociclib. The mammalian target of rapamycin inhibitor everolimus may be administered with exemestane to post-menopausal women with MBC whose disease progresses while receiving nonsteroidal AIs (6).

ESMO Guidelines (2018) state that combination of an endocrine agent (AI, tamoxifen or fulvestrant) with everolimus has shown a PFS benefit, albeit without a statistically significant OS (overall survival) benefit in the second-line setting and, more recently, also in the first-line setting, and is an available option for patients previously exposed to ET (endocrine therapy). Its use is associated with substantial toxicity, which downgrades its ESMO-MCBS score to 2. However, as more experience is gained regarding the use of everolimus and the management of its toxicities, its clinical use becomes easier, in particular regarding management of mucositis. Adequate prevention, close monitoring and proactive treatment of adverse events is needed, particularly in older patients treated with everolimus due to the increased incidence of toxic deaths reported in the BOLERO-2 trial. Tamoxifen or fulvestrant can also be combined with everolimus. The optimal sequence of endocrine-based therapy is uncertain. It depends on which agents were previously used [in the (neo)adjuvant or advanced settings], the burden of the disease, patient's preference, costs and availability. Available options [for pre- and peri-menopausal women with OFS/OFA (ovarian function suppression or ablation), men (preferably with LHRH agonist) and post-menopausal women] include AI, tamoxifen, fulvestrant, AI/fulvestrant + CDK 4/6 inhibitor, AI/tamoxifen/fulvestrant + everolimus. In later lines, also megestrol acetate and oestradiol, as well as repetition of previously used agents, may be used (7).

NCCN Guidelines (2018) includes everolimus + exemestane, everolimus + tamoxifen and everolimus + fulvestrant in the list of preferred therapies for post-menopausal women with ER+ and/or PR+ and HER2- recurrent or Stage IV disease (8).

Treatment continuation

How would treatment success be defined or measured?

Patients would be treated until disease progression

What is the average length of treatment required before determining treatment response?

Treatment would be evaluated on a regular basis

What other interventions would be needed in the event of treatment-related adverse events?

Management of severe and/or intolerable suspected adverse reactions may require dose reduction and/or temporary interruption of therapy. For adverse reactions of Grade 1, dose adjustment is usually not required. If dose reduction is required, the recommended dose is 5 mg daily and must not be lower than 5 mg daily (1).

- Stomatitis, including mouth ulcerations and oral mucositis, is the most commonly reported adverse reaction and it mostly occurs within the first 8 weeks of treatment. Management of stomatitis may therefore include prophylactic and/or therapeutic use of topical treatments, such as an alcohol-free corticosteroid oral solution as a mouthwash. Products containing alcohol, hydrogen peroxide, iodine and thyme derivatives should be avoided as they may exacerbate the condition. Monitoring for and treatment of fungal infection is recommended, especially in patients being treated with steroid-based medications (1).
- Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens. Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis, candidiasis or pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) and viral infections including reactivation of hepatitis B virus, have been reported. Some of these infections have been severe (e.g. leading to sepsis, respiratory or hepatic failure) and occasionally fatal. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment. If a diagnosis of invasive systemic fungal infection is made, treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy (1).
- Non-infectious pneumonitis (including interstitial lung disease) has been frequently reported. Some cases were severe and on rare occasions, a fatal outcome was observed. If symptoms are moderate (Grade 2) or severe (Grade 3) the use of corticosteroids may be indicated until clinical symptoms resolve. For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) may be considered (1).
- Dyslipidaemia (including hypercholesterolaemia and hypertriglyceridaemia) has been reported necessitating monitoring of blood cholesterol and triglycerides prior to the start of therapy and periodically thereafter, as well as management with appropriate medical therapy (1).
- Decreased haemoglobin, lymphocytes, neutrophils and platelets have been reported and monitoring of complete blood count is recommended prior to the start of therapy and periodically thereafter (1).

A summary of strategies for management of adverse events is included in the paper by Petersen included with the references (9).

Prescribing and dispensing

Should initiation of this therapy be limited to certain prescriber types? If so, please explain why.

Medical oncologist

If starting this therapy was limited to certain prescriber types, would it be appropriate for ongoing prescribing to be managed by a wider group of prescribers? If so, who?

No

Are there any other issues that PHARMAC should be aware of in relation to the administration of this pharmaceutical, such as infusion time, compounding requirements or safety issues?

No

Health need

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications.

What is the health need of people with the indication(s) for which funding is sought? Please include details of whether reduced life expectancy could be expected or details of potential loss of quality of life including the cause of this loss.

Over 3300 people are diagnosed with breast cancer each year in New Zealand and over 600 people will die from this disease. Advanced Breast Cancer (ABC) is cancer that is locally invasive (Stage III) and is not amenable to surgery or radiotherapy of curative intent **or** has metastasised from its primary location in the tissues of the breast to other tissues (Stage IV), most often bones, brain, lungs, or liver. ABC adversely impacts health-related quality of life (HR-QoL), both through physical symptoms and psychosocial distress. The key therapy goals for patients with ABC are focused on delaying progression and prolonging survival without compromising HR-QoL.

Is there an unmet health need in the populations that may potentially receive benefit from this treatment? If so, please explain.

Although there have been improvements in rates of survival over the past decades, New Zealand still lags behind some other countries (10). For people who have advanced breast cancer, extension of, and quality of, life are key priorities. BCAC and other patient groups such as Metavivors are concerned about poor access to treatment in New Zealand for people with advanced breast cancer. Better access to treatments that are aimed at controlling symptoms, improving or maintaining quality of life and prolonging survival is needed. ER positive breast cancer is the most common type of breast cancer (70-80%). Limitations of current endocrine therapy are intrinsic and acquired drug resistance. The availability of an alternate agent such as everolimus, which targets a different pathway from existing treatments, could delay or prevent the need for chemotherapy in ABC.

Are there sub-populations within these populations that have a higher health need?

Māori and Pacific women have poorer survival and are therefore more likely to be affected by metastatic disease as well as having more co-morbidities (11-13). Late diagnosis, deprivation and differential access to and quality of cancer care services are key contributors to ethnic disparities in breast cancer survival in New Zealand (14). Patients treated in the private health care sector in New Zealand have better survival from breast cancer compared with those in public care (15). Currently people with financial means are able to access everolimus treatment whereas others cannot.

What are the treatments that patients with these indications currently receive, if any? Please describe the dose, duration of treatment, along with the risks and benefits associated with this treatment.

Tamoxifen and aromatase inhibitors (AIs) are the traditional endocrine therapy standard of care. The only remaining option once endocrine therapies are no longer efficacious is cytotoxic chemotherapy that impacts day to day functioning and quality of life.

Are there any issues regarding the availability or suitability of existing treatments for this indication?

Endocrine therapies target ER signalling and represent the backbone of adjuvant and first-line therapy of post-menopausal women with ER+ HER2- ABC. AIs work by reducing circulating oestrogen, however the tumour cell typically develops resistance to AIs, such that the ER can still drive tumour growth even in the absence of oestrogen. Intrinsic and acquired resistance to endocrine therapy is a significant clinical problem for ABC, with all ER+ tumours eventually becoming endocrine therapy-resistant resulting in disease progression.

Would the pharmaceutical replace or complement these existing treatments? Please explain.

Endocrine therapy is the cornerstone of treatment for patients with hormone-receptor (HR)‑positive advanced breast cancer with aromatase inhibitors used in first-line therapy. However, not all patients respond to first-line endocrine therapy (primary or de novo resistance), and even patients who have a response will eventually relapse (acquired resistance). The study of resistance to endocrine therapies in HR-positive breast cancer has aimed at identifying new therapeutic strategies that would enhance the efficacy of endocrine therapies. An emerging mechanism of endocrine resistance is aberrant signalling through the phosphatidylinositol 3-kinase (PI3K)‑Akt‑mammalian target of rapamycin (mTOR) signalling pathway. Growing evidence supports a close interaction between the mTOR pathway and ER signalling. A substrate of mTOR complex 1 (mTORC1), called S6 kinase 1, phosphorylates the activation function domain 1 of the ER, which is responsible for ligand-independent receptor activation. Everolimus inhibits mTOR through allosteric binding to mTORC1. The BOLERO-2 study showed the benefit of combined therapy with exemestane and everolimus (16). The addition of everolimus would therefore complement and augment outcomes from existing treatment and offers another choice for those who have advanced on standard first line treatments.

Does this indication disproportionately affect any populations that may already be experiencing a health disparity?

Māori women have one of the highest incidences of breast cancer in the world (17). Māori and Pacific women have poorer survival and are therefore more likely to be affected by ABC as well as having more co-morbidities (11-13). Māori women are less likely to adhere to long-term adjuvant endocrine therapy (17). Patients from lower socioeconomic groups have poorer survival statistics and therefore may benefit from subsidy of a wider range of treatment alternatives (15).

Health need

Is there an unmet health need in other people due to the indication, such as in people who care for or live with those with the indication, or from spread of disease?

Families and whanau are integral to the patient's life journey at this stage of disease. ABC also poses a burden on caregivers; 69% of caregivers of women with ABC report some kind of adverse impact on their work. In addition to the impact on their day-to-day lives, caregivers report increases in depression and perceived burden as the patients' functional status declines. At the start of the terminal period of the patients' disease, 30% of caregivers reported being depressed (18).

Health benefits and risks in the indication(s) for which funding is sought

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications.
Discuss the potential benefits from treatment with the pharmaceutical compared with current treatment options (if any).

See next pages

Evidence for Everolimus+Exemestane (BOLERO-2)

Subsequent Open Label Observational Studies using the Combination of Everolimus and Exemestane

Studies that Used a Combination of Exemestane and Other Anti-Oestrogen Therapies including Anastrazole, Tamoxifen and Letrozole

BOLERO-2 – Breast Cancer Trial of Oral Everolimus-2

Main Publication and Basis for Regulatory Approvals in Europe, USA and Australia

In this phase 3, randomised trial, 724 patients with hormone-receptor-positive advanced breast cancer who had recurrence or progression while receiving previous therapy with a nonsteroidal aromatase inhibitor (NSAI) in the adjuvant setting or with advanced disease (or both) were randomly assigned to everolimus and exemestane versus exemestane and placebo (in a 2:1 ratio). The primary end point was progression-free survival. Secondary end points included survival, response rate, and safety. A pre-planned interim analysis was performed by an independent data and safety monitoring committee after 359 progression-free survival events were observed. The median age was 62 years, 56% had visceral involvement, and 84% had hormone-sensitive disease. Previous therapy included letrozole or anastrozole (100%), tamoxifen (48%), fulvestrant (16%), and chemotherapy (68%). The most common grade 3 or 4 adverse events were stomatitis (8% in the everolimus-plus-exemestane group vs. 1% in the placebo-plus-exemestane group), anaemia (6% vs. <1%), dyspnoea (4% vs. 1%), hyperglycaemia (4% vs. <1%), fatigue (4% vs. 1%), and pneumonitis (3% vs. 0%). At the interim analysis, median progression-free survival was 6.9 months with everolimus plus exemestane and 2.8 months with placebo plus exemestane, according to assessments by local investigators (HR for progression or death, 0.43; 95% CI, 0.35 to 0.54; p<0.001). Median progression-free survival was 10.6 months and 4.1 months, respectively, according to central assessment (HR, 0.36; 95% CI, 0.27 to 0.47; p<0.001). It was concluded that everolimus combined with an aromatase inhibitor improved progression-free survival in patients with hormone-receptor-positive advanced breast cancer previously treated with nonsteroidal aromatase inhibitors (16).

Final PFS Analysis

Final study results with median 18-month follow-up showed that median PFS remained significantly longer with everolimus plus exemestane versus placebo plus exemestane [investigator review: 7.8 versus 3.2 months, respectively; HR = 0.45 (95% confidence interval 0.38-0.54); log-rank p<0.0001; central review: 11.0 versus 4.1 months, respectively; HR=0.38 (95% CI 0.31-0.48); log-rank p<0.0001] in the overall population and in all prospectively defined subgroups, including patients with visceral metastases, [corrected] and irrespective of age. The incidence and severity of adverse events were consistent with those reported at the interim analysis and in other everolimus trials. It was concluded that the addition of everolimus to exemestane markedly prolonged PFS in patients with HR(+) advanced BC with disease recurrence/progression following prior NSAIs. These results further support the use of everolimus plus exemestane in this patient population (4).

HRQoL

This publication reported the treatment effects on health-related quality of life (HRQOL) in BOLERO-2. Using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) questionnaire, HRQOL was assessed at baseline and every 6 weeks thereafter until disease progression and/or treatment discontinuation. The 30 items in 15 subscales of the QLQ-C30 include global health status wherein higher scores (range, 0-100) indicate better HRQOL. This analysis included a protocol-specified time to definitive deterioration (TDD) analysis at a 5% decrease in HRQOL versus baseline, with no subsequent increase above this threshold. The authors reported additional sensitivity analyses using 10-point minimal important difference decreases in the global health status score versus baseline. Treatment arms were compared using the stratified log-rank test and Cox proportional hazards model adjusted for trial stratum (visceral metastases, previous hormone sensitivity), age, sex, race, baseline global health status score and ECOG performance status, prognostic risk factors, and treatment history. Baseline global health status scores were found to be similar between treatment groups (64.7 vs 65.3). The median TDD in HRQOL was 8.3 months with EVE + EXE versus 5.8 months with PBO + EXE (HR, 0.74; p=0.0084). At the 10-point minimal important difference, the median TDD with EVE + EXE was 11.7 months versus 8.4 months with PBO + EXE (HR,

0.80; P = .1017). In conclusion, in patients with advanced breast cancer who develop disease progression after treatment with nonsteroidal aromatase inhibitors, EVE + EXE was associated with a longer TDD in global HRQOL versus PBO + EXE (19).

Post hoc analyses on HRQoL

HRQOL was assessed using EORTC QLQ-C30 and QLQ-BR23 questionnaires at baseline and every 6 weeks thereafter until treatment discontinuation because of disease progression, toxicity, or consent withdrawal. Endpoints included the QLQ-C30 Global Health Status (QL2) scale, the QLQ-BR23 breast symptom (BRBS), and arm symptom (BRAS) scales. Between-group differences in change from baseline were assessed using linear mixed models with selected covariates. Sensitivity analysis using pattern-mixture models determined the effect of study discontinuation on/before week 24. Treatment arms were compared using differences of least squares mean (LSM) changes from baseline and 95% confidence intervals (CIs) at each time point and overall. Linear mixed models (primary model) demonstrated no statistically significant overall difference between EVE + EXE and PBO + EXE for QL2 (LSM difference = -1.91; 95% CI =-4.61, 0.78), BRBS (LSM difference = -0.18; 95% CI = -1.98, 1.62), or BRAS (LSM difference = -0.42; 95% CI = -2.94, 2.10). Based on pattern-mixture models, patients who dropped out early had worse QL2 decline on both treatments. In the expanded pattern-mixture model, EVE + EXE-treated patients who did not drop out early had stable BRBS and BRAS relative to PBO + EXE. It was concluded that EVE + EXE provides clinical benefit without adversely impacting HRQOL in patients with HR(+) ABC who recurred/progressed on prior NSAIs versus endocrine therapy alone (20).

Overall Survival

OS was a key secondary end point in BOLERO-2 that was reported separately. At the time of data cut-off (3 October 2013), 410 deaths had occurred and 13 patients remained on treatment. Median OS in patients receiving EVE + EXE was 31.0 months [95% confidence interval (CI) 28.0-34.6 months] compared with 26.6 months (95% CI 22.6-33.1 months) in patients receiving PBO + EXE (HR = 0.89; 95% CI 0.73-1.10; log-rank P=0.14). Post-study treatments were received by 84% of patients in the EVE + EXE arm versus 90% of patients in the PBO + EXE arm. Types of post-study therapies were balanced across arms, except for chemotherapy (53% EVE + EXE versus 63% PBO + EXE). No new safety concerns were identified. In BOLERO-2, adding EVE to EXE did not confer a statistically significant improvement in the secondary end point OS despite producing a clinically meaningful and statistically significant improvement in the primary end point, PFS (4.6-months prolongation in median PFS; P < 0.0001) (21).

Adverse Events

This publication focussed on safety which included recording of AEs, laboratory values, dose interruptions/adjustments, and study drug discontinuations. The safety population comprised 720 patients (EVE + EXE, 482; PBO + EXE, 238). The median follow-up was 18 months. Class-effect toxicities, including stomatitis, pneumonitis, and hyperglycaemia, were generally of mild or moderate severity and occurred relatively early after treatment initiation (except pneumonitis); incidence tapered off thereafter. EVE dose reduction and interruption (360 and 705 events, respectively) required for AE management were independent of patient age. The median duration of dose interruption was 7 days. Discontinuation of both study drugs because of AEs was higher with EVE + EXE (9%) versus PBO + EXE (3%). In conclusion, most EVE-associated AEs occur soon after initiation of therapy, are typically of mild or moderate severity, and are generally manageable with dose reduction and interruption. Discontinuation due to toxicity was uncommon (22).

Subgroup Analyses of BOLERO-2

Visceral Metastases: This pre-specified exploratory subgroup analysis evaluated the efficacy and safety of EVE+EXE versus PBO+EXE in a prospectively defined subgroup of patients with visceral metastases. At a median follow-up of 18 months, EVE+EXE significantly prolonged median PFS compared with PBO+EXE both in patients with visceral metastases (N=406; 6.8 versus 2.8 months) and in those without visceral metastases (N=318; 9.9 versus 4.2 months). Improvements in PFS with EVE+EXE versus PBO+EXE were also observed in patients with visceral metastases regardless of ECOG performance status. Patients with visceral metastases and ECOG PS 0 had a median PFS of 6.8 months with EVE+EXE versus 2.8 months with PBO+EXE. Among patients with visceral metastases and ECOG PS >/=1, EVE+EXE treatment more than tripled median PFS compared with PBO+EXE (6.8 versus 1.5 months). In conclusion, adding EVE to EXE markedly extended PFS by >/=4 months among patients with HR+ HER2- ABC regardless of the presence of visceral metastases (23).

Genetic Status of Cancer-related genes: Progression-free survival benefit with everolimus was maintained regardless of alteration status of PIK3CA, FGFR1, and CCND1 or the pathways of which they are components. However, quantitative differences in everolimus benefit were observed between patient subgroups defined by the exon-specific mutations in PIK3CA (exon 20 v 9) or by different degrees of chromosomal instability in the tumour tissues. In conclusion, data from this exploratory analysis suggested that the efficacy of everolimus was largely independent of the most commonly altered genes or pathways in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer (24).

Asian versus non-Asian Patients: Safety and efficacy results from Asian versus non-Asian patients in BOLERO-2 were reported. Of 143 Asian patients, 98 received EVE + EXE and 45 received PBO + EXE. Treatment with EVE + EXE significantly improved median PFS versus PBO + EXE among Asian patients by 38 % (HR = 0.62; 95 % CI, 0.41-0.94). Median PFS was also improved among non-Asian patients by 59 % (HR = 0.41; 95 % CI, 0.33-0.50). Median PFS duration among EVE-treated Asian patients was 8.48 versus 4.14 months for PBO + EXE, and 7.33 versus 2.83 months, respectively, in non-Asian patients. The most common grade 3/4 adverse events (stomatitis, anaemia, elevated liver enzymes, hyperglycaemia, and dyspnoea) occurred at similar frequencies in Asian and non-Asian patients. Grade 1/2 interstitial lung disease occurred more frequently in Asian patients. Quality of life was similar between treatment arms in Asian patients. It was concluded that adding EVE to EXE provided substantial clinical benefit in both Asian and non-Asian patients with similar safety profiles. This combination represents an

improvement in the management of post-menopausal women with HR(+)/HER2(-) advanced breast cancer progressing on nonsteroidal aromatase inhibitors, regardless of ethnicity (25)

Elderly Patients: This analysis compared safety and efficacy data in elderly subsets (>/= 65 years, n = 275; >/= 70 years, n = 164) and found results were generally comparable with younger patients. The addition of EVE to EXE improved PFS regardless of age (HR, 0.59 [>/= 65 years] and 0.45 [>/= 70 years]). Adverse events (AEs) of special interest (all grades) that occurred more frequently with EVE than with PBO included stomatitis, infections, rash, pneumonitis, and hyperglycaemia. Elderly EVE-treated patients had similar incidences of these AEs as did younger patients but had more on-treatment deaths. Careful monitoring and appropriate dose reductions or interruptions for AE management are recommended during treatment with EVE in this patient population (26).

First Line Setting: This exploratory analysis included the subgroup of patients in BOLERO-2 whose last treatment before study entry was in the (neo)adjuvant setting. Overall, 137 patients received first-line EVE + EXE (n = 100) or PBO + EXE (n = 37). Median PFS by local investigator assessment nearly tripled to 11.5 months with EVE + EXE from 4.1 months with PBO + EXE (HR = 0.39; 95 % CI 0.25-0.62), while maintaining quality of life. This was confirmed by central assessment (15.2 vs 4.2 months; HR = 0.32; 95 % CI 0.18-0.57). The marked PFS improvement in patients receiving EVE + EXE as first-line therapy for disease recurrence during or after (neo)adjuvant NSAI therapy supports the efficacy of this combination in the first-line setting (27).

Summaries of Observational Studies Reported Based on the BOLERO-2 regimen

- Post-menopausal women with HR-positive HER2-negative advanced breast cancer progressing after prior non-steroidal aromatase inhibitors (NSAIs) were included in the BALLET trial. The objectives of this report were to evaluate the safety profile of this combination in a subset of Spanish patients in the BALLET trial and to characterise grade 3 and 4 adverse events (AEs) in routine clinical practice in Spain. Between September 2012 and July 2013, 429 patients (20% of the overall study population) were included in the BALLET study in 52 hospitals in Spain, of whom 100 (23%) were >/= 70 years. The median treatment duration was 3.14 and 3.03 months for exemestane and everolimus, respectively. The most common reasons for discontinuation of treatment were local reimbursement of everolimus (43%), followed by disease progression (31%) and the incidence of AEs (15%). The most frequent AEs causing permanent discontinuation were pneumonitis (4%), asthenia (2%) and stomatitis (2%). Overall, 87% of patients experienced at least one AE of any grade, 30% of patients at least one grade 3 AE and 2% of patients a grade 4 AE. It was concluded that the safety profile in Spanish patients of the BALLET trial is consistent with the results obtained in the overall population of the trial, as well as in previous clinical trials (28).
- The EVA study collected data on efficacy and safety of EVE-EXE combination in the clinical setting, as well as exploring efficacy according to EVE Dose-Intensity (DI) and to previous treatment with fulvestrant. This study aimed to describe the outcome of ABC pts treated with EVE-EXE combination in terms of median duration of EVE treatment and ORR in a real-life setting. From July 2013 to December 2015, the EVA study enrolled 404 pts. Median age was 61 years (33-83). Main metastatic sites were: bone (69.1%), soft tissue (34.7%) and viscera (33.2%). Median number of previous treatments was 2 (1-7). 43.3% of the pts had received Fulvestrant. Median exposure to EVE was 31.0 weeks (15.4-58.3) in the whole population. No difference was observed in terms of EVE exposure duration according to DI (p for trend = 0.27) or type of previous treatments (p=0.33). ORR and Disease Control Rate (DCR) were observed in 31.6% and 60.7% of the patients, respectively, with the lowest ORRs confined in CHT pre-treated patients or in those who received the lowest DI of EVE. Grade 3-4 adverse events (AEs) were reported in 37.9% of the patients. Main AEs were: stomatitis (11.2%), non-infectious pneumonitis - NIP (3.8%), anaemia (3.8%) and fatigue (3.2%). The EVA study provided new insights in the use of EVE-EVE combination in HR+ ABC pts many years after the publication of the pivotal trial. The combination is safe and the best response could be obtained in patients receiving the full dose of EVE and/or after hormone-therapy such as fulvestrant in ABC (29).
- The open-label, single-arm, phase IIIB 4EVER trial evaluated the clinical effectiveness of everolimus plus exemestane in post-menopausal women with HR+, HER2- ABC who had progressed on or after an NSAI, but with no restrictions on the time of progression after NSAI, prior chemotherapy for advanced disease, or previous exemestane. The primary endpoint was overall response rate (ORR; i.e. the percentage of patients with a best overall response of complete or partial response per RECIST 1.1) within the first 24 weeks of treatment. Secondary endpoints included PFS, overall survival, safety, and health-related quality of life. Between June 2012 and November 2013, 299 patients were enrolled at 82 German centres: 281 patients were evaluable for efficacy and 299 for safety. The ORR was 8.9% (95% confidence interval [CI]: 5.8-12.9%). Median PFS was 5.6 months (95% CI: 5.4-6.0 months). The most frequent grade 3/4 adverse events were stomatitis (8.4%), general physical health deterioration (6.7%), dyspnoea (4.7%), and anaemia (4.3%). The ORR in 4EVER was lower than in BOLERO-2, likely due to inclusion of patients with more advanced disease and extensive pre-treatment. These data confirm the clinical benefits and known safety profile of everolimus plus exemestane in post-menopausal women with HR+, HER2- ABC (30).
- A retrospective Italian analysis examined the efficacy of the EVE/EXE combination in terms of PFS and RR related to dose intensity (5 mg daily versus 10 mg daily) and tolerability. It included 163 HER2-negative ER+/PgR+ ABC patients, treated with EVE/EXE from May 2011 to March 2016, were included in the analysis. The primary endpoints were the correlation between the daily dose and RR and PFS, as well as an evaluation of the tolerability of the combination. Secondary endpoints were RR, PFS, and OS according to the line of treatment. Patients were classified into three

different groups, each with a different dose intensity of everolimus (A, B, C). RR was 29.8% (A), 27.8% (B) (p=0.953), and not evaluable (C). PFS was 9 months (95% CI 7-11) (A), 10 months (95% CI 9-11) (B), and 5 months (95% CI 2-8) (C), p=0.956. OS was 38 months (95% CI 24-38) (A), median not reached (B), and 13 months (95% CI 10-25) (C), p=0.002. Adverse events were stomatitis 57.7% (11.0% grade 3-4), asthenia 46.0% (6.1% grade 3-4), hypercholesterolemia 46.0% (0.6% grade 3-4), and hyperglycaemia 35.6% (5.5% grade 3-4). The main reason for discontinuation/interruption was grade 2-3 stomatitis. No correlation was found between dose intensity (5 vs. 10 mg labelled dose) and efficacy in terms of RR and PFS. The tolerability of the higher dose was poor, although this had no impact on efficacy (31). This Italian group also reported clinical data from 181 consecutive patients. Due to toxic events, everolimus dosage was reduced to 5 mg in 27% of patients. No association was found in the analysis between toxicity and number of prior therapies, neither between toxicity and response. In the multivariate analysis the previous exposure to anthracyclines for advanced disease represents the only predictive factor of developing grade >/=2 toxicity (OR = 2.85 CI 95% 1.07-7.59, p=0.036). The combination of everolimus and exemestane was found to be a safe and effective treatment for endocrine sensitive MBC patients in routine clinical practice. The rate of treatment discontinuation due to toxicity was low and none association between previous number of treatments and response or between toxicity and response was found (32).

- French practice with everolimus was evaluated 2 years after the French marketing authorisation (July 2012). This study included 123 consecutive patients treated with everolimus combined with endocrine treatment in two French Cancer Centres. All patients had luminal (ER positive, HER2 negative) BC and had been previously treated with endocrine therapy for advanced disease. The median age at initiation of everolimus was 63 y (36-84). Median delay from cancer diagnosis to everolimus was 12.6 years (1.3-34.8). Grade 2 or 3 side effects were experienced by 49.6% and 32.5% of the patients, respectively. Most frequent side effects were grade 2/3 mucositis (32.6%/11.2%), grade 1/2 decreased appetite (24.4%/13.8%), and grade 1/2 rash (28.5%/13.8%). At a median follow up of 10 months, median progression free survival was 9 months (Range 0.4 to 26+ months), and median overall survival was 21 months (Range 0.4 to 26+ months). It was concluded that, in routine practice, everolimus efficacy appears very close to the BOLERO-2 results, although in more heavily pre-treated patients. Everolimus based therapy appears feasible and side effects are similar to those previously reported. These data support the use of everolimus in daily practice (33).
- A Chinese real-world practice study evaluated the efficacy and safety of everolimus plus endocrine therapy and investigated factors associated with efficacy. This retrospective study included 75 HR+/HER2- MBC patients who received everolimus plus endocrine therapy after progression on prior endocrine therapy in Fudan University Shanghai Cancer Center (FUSCC) between June 2013 and February 2016. Main outcome measures are progression free survival (PFS), overall survival (OS), objective response rate (ORR), clinical benefit rate (CBR) and safety profile. After a median follow up of 10.3 (range: 2.1-32.2) months, median PFS was 5.9 months (95%CI, 4.6-7.2), and median OS was not reached. The CBR was 38.8% (95%CI, 26.8-50.8) and ORR was 9.0% (95%CI, 2.0-16.0). Most common all-grade adverse events were stomatitis (57.1%), fatigue (25.7%), infection (24.3%) and hyperglycaemia (21.4%). The most common >/=3 grade adverse events were stomatitis (9.3 %) and thrombocytopenia (5.7%). No treatment-related death was documented during and one month after the drug administration. The safety profiles were similar to previous studies but incidences were lower. In conclusion, everolimus combined with endocrine therapy provides a reasonable option for Chinese HR+/HER2- metastatic breast cancer patients (34)
- Another report from France examined 63 MBC patients who progressed under hormonotherapy (HT; n = 30) or after chemotherapy (CT; n = 32) received everolimus plus HT (EHT) and were analysed for safety, efficacy and overall survival (OS). This cohort was compared with a previous cohort of 530 MBC patients stratified by line. The median duration of EHT was 27.8 weeks at 5-10 mg/day until clinical progression or toxicity. Median OS was not reached (median follow-up 18 months). Twelve-month survival was 100, 79 and 49% for patients treated with 0 (n = 13), 1-2 (n = 18) and >3 CT (n = 32), respectively. Median time-to-treatment failure was 6.4 months. In 62 EHT patients randomly matched 1:7 with 421 previous patients for age and number of CT, OS improved compared with patients receiving a new CT (p=0.062). In patients pre-treated with <2 CT, EHT gave a better OS than in those with a new CT (p=0.026). These results support the use of EHT whatever the number of previous lines (35).
- This study described frequency and timing of everolimus dose reductions and/or interruptions due to adverse events. It was a single-center retrospective case series including all patients who received everolimus in combination with exemestane from May 1, 2012, through July 31, 2013. The primary objective was to determine the incidence of first-cycle interruptions or dose reductions with everolimus. Forty-six patients were included in the analysis. First-cycle dose reductions or interruptions were observed in 21 (45.6 %) patients. The most common adverse events leading to dose reduction or interruption was stomatitis (57.1 %), fatigue (14.3 %), and diarrhoea (14.3 %). The median time to dose reduction was 14 days, and the median duration of the interruption was 14 days. The median progression-free survival was 6.2 months, and the median time to treatment failure was 4.4 months. In summary, almost half of the patients treated with everolimus and exemestane required a dose reduction or interruption of everolimus during the first cycle of treatment. This early onset of adverse events requires thorough patient education and close clinical monitoring during the first 28 days of therapy (36).
- An Indian retrospective analysis was undertaken of MBC patients who had recurrence or progression while receiving aromatase inhibitors (AI's) and further treated with everolimus and either tamoxifen/AI/fulvestrant between March 2012 and June 2014. There were 41 patients with median age 55 years, 73% with visceral metastases, and 73% with >/=2 sites of metastases. Thirty (73%) patients had received 3 prior lines of therapy including AI (100%), tamoxifen

(94%), fulvestrant (39%), and chemotherapy (100%) while the remaining had received <3 lines of prior therapy. The commonest Grade 3/4 adverse events were stomatitis (19%), hyperglycaemia (new/worsening, 17%), fatigue (14.5%), non-neutropenic infections (14%), anaemia (12%) and pneumonitis (7%). Everolimus dose reductions were required in 31% patients. There were 30% partial responses, 38% prolonged disease stabilisations and 32% disease progression as best responses to everolimus. The median progression-free survival was 22 weeks (5 months). Everolimus based treatment has meaningful activity in heavily pre-treated patients with HR-positive MBC but was associated with considerable toxicity and requirement for dose adjustment (37).

Everolimus in Combination with Other Anti-oestrogen Therapy

Everolimus Plus Tamoxifen (TAMRAD Study)

This open-label, phase II study conducted by the GINECO (Groupe d'Investigateurs Nationaux pour l'Etude des Cancers de l'Ovaire et du Sein) evaluated efficacy and safety of everolimus in combination with tamoxifen in patients with MBC resistant to aromatase inhibitors (AIs). post-menopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative, AI-resistant MBC were randomly assigned to tamoxifen 20 mg/d plus everolimus 10 mg/d (n = 54) or tamoxifen 20 mg/d alone (n = 57). Randomisation was stratified by primary and secondary hormone resistance. Primary end point was clinical benefit rate (CBR), defined as the percentage of all patients with a complete or partial response or stable disease at 6 months. No formal statistical comparison between groups was planned. The 6-month CBR was 61% (95% CI, 47 to 74) with tamoxifen plus everolimus and 42% (95% CI, 29 to 56) with tamoxifen alone. Patients with secondary resistance seemed to exhibit more benefit with tamoxifen plus everolimus than patients with primary resistance (CBR: 74% v 48% [secondary resistance]; 46% v 36% [primary resistance]). Time to progression (TTP) increased from 4.5 months with tamoxifen alone to 8.6 months with tamoxifen plus everolimus, corresponding to a 46% reduction in risk of progression with the combination (HR 0.54; 95% CI, 0.36 to 0.81; exploratory p<0.002). Similar to CBR, the TTP benefits seemed to be more prominent in patients with secondary resistance. Risk of death was reduced by 55% with tamoxifen plus everolimus versus tamoxifen alone (HR, 0.45; 95% CI, 0.24 to 0.81; exploratory p<0.007). The main toxicities associated with tamoxifen plus everolimus were fatigue (72% v 53% with tamoxifen alone), stomatitis (56% v 7%), rash (44% v 7%), anorexia (43% v 18%), and diarrhoea (39% v 11%). In conclusion, this randomized phase II trial suggests that tamoxifen combined with everolimus may reverse hormone resistance and lead to increased CBR, TTP, and OS compared with tamoxifen alone in post-menopausal women with AI-resistant MBC, particularly those with secondary hormone resistance. The observed toxicities were manageable and consistent with those of previous studies. (38).

Everolimus Plus Anastrozole

This study evaluated combined anastrozole and everolimus in 55 patients with metastatic oestrogen (ER) and/or progesterone receptor (PR)-positive breast and gynaecologic tumours. Endpoints were safety, antitumor activity and molecular correlates. Full doses of anastrozole (1 mg PO daily) and everolimus (10 mg PO daily) were well tolerated. Twelve of 50 evaluable patients (24%) (median = 3 prior therapies) achieved stable disease (SD) >/= 6 months/partial response (PR)/complete response (CR) (n = 5 (10%) with PR/CR): 9 of 32 (28%) with breast cancer (n=5 (16%) with PR/CR); 2 of 10 (20%), ovarian cancer; and 1 of 6 (17%), endometrial cancer. Six of 22 patients (27%) with molecular alterations in the PI3K/AKT/mTOR pathway achieved SD >/= 6 months/PR/CR. Six of 8 patients (75%) with SD >/= 6 months/PR/CR with molecular testing demonstrated at least one alteration in the PI3K/AKT/mTOR pathway: mutations in PIK3CA (n=3) and AKT1 (n=1) or PTEN loss (n=3). All three responders (CR (n = 1); PR (n=2)) who had next generation sequencing demonstrated additional alterations: amplifications in CCNE1, IRS2, MCL1, CCND1, FGFR1 and MYC and a rearrangement in PRKDC. It was concluded that combination anastrozole and everolimus is well tolerated at full approved doses, and is active in heavily pre-treated patients with ER and/or PR-positive breast, ovarian and endometrial cancers. Responses were observed in patients with multiple molecular aberrations (39).

Everolimus Plus Letrozole

This study investigated the clinical benefit of combining everolimus with a different endocrine partner, letrozole. In this phase II, open-label, single-arm, multicenter trial, post-menopausal women with HR(+), HER2(-) ABC who had recurrence/progression on/after prior ET received everolimus 10 mg daily and letrozole 2.5 mg daily. The primary end point was objective response rate; key secondary end points included disease-control rate, PFS, overall survival, and safety. A total of 72 patients were enrolled and followed-up for a median duration of 11.4 months. Everolimus plus letrozole achieved an overall response rate of 23.3% (95% confidence interval [CI], 13.4%-36.0%). The median PFS was 8.8 months (95% CI, 6.6-11.0 months), and the overall survival was 22.9 months (95% CI, 18.5-28.9 months). Disease-control rate was achieved in 51 (85%) patients. The safety profile was consistent with previously published data: The most frequently reported any grade adverse events (AEs) were fatigue (61.1%), stomatitis (54.2%), and rash (33.4%). The most frequently reported grade 3 AEs were stomatitis and anaemia (8.3% each), fatigue and diarrhoea (5.6% each), and hyperglycaemia (4.2%). Only 1 patient had grade 4 AE of anaemia. It was concluded that everolimus plus letrozole demonstrated clinical benefit and could be a valid treatment option for post-menopausal women recurring/progressing on prior endocrine therapy (40).

Everolimus Plus Fulvestrant

Kornblum et al. recently reported on the use of everolimus plus the selective ER down-regulator fulvestrant, on the basis that this combination might be more efficacious than fulvestrant alone in ER-positive metastatic breast cancer resistant to aromatase inhibitor (AI) therapy. This randomised, double-blind, placebo-controlled, phase II study included 131 post-menopausal women

with ER-positive, human epidermal growth factor receptor 2–negative, AI-resistant metastatic breast cancer randomly assigned to fulvestrant (500 mg days 1 and 15 of cycle 1, then day 1 of cycles 2 and beyond) plus everolimus or placebo. The study was designed to have 90% power to detect a 70% improvement in median progression-free survival from 5.4 months to 9.2 months. Secondary end points included objective response and clinical benefit rate (response or stable disease for at least 24 weeks). Prophylactic corticosteroid mouth rinses were not used. The addition of everolimus to fulvestrant improved the median progression-free survival from 5.1 to 10.3 months (HR, 0.61 [95% CI, 0.40 to 0.92]; stratified log-rank p=0.02), indicating that the primary trial end point was met. Objective response rates were similar (18.2% v 12.3%; p=0.47), but the clinical benefit rate was significantly higher in the everolimus arm (63.6% v 41.5%; p=0.01). Adverse events of all grades occurred more often in the everolimus arm, including oral mucositis (53% v 12%), fatigue (42% v 22%), rash (38% v 5%), anaemia (31% v. 6%), diarrhoea (23% v 8%), hyperglycaemia (19% v 5%), hypertriglyceridemia (17% v 3%), and pneumonitis (17% v 0%), although grade 3 to 4 events were uncommon. It was concluded that everolimus enhances the efficacy of fulvestrant in AI-resistant, ER-positive metastatic breast cancer (41).

BOLERO-4 – 1st and 2nd line treatment settings

The recently published BOLERO-4 study investigated the combination of everolimus plus endocrine therapy in first-line and second-line treatment settings for post-menopausal women with oestrogen receptor-positive, human epidermal growth receptor 2-negative advanced breast cancer. This multicentre, open-label, single-arm, phase 2 BOLERO-4 (Breast Cancer Trials of Oral Everolimus) clinical trial, screened 245 patients for eligibility; and 202 were enrolled between March 7, 2013, and December 17, 2014. A median follow-up of 29.5 months had been achieved by the data cut-off date (December 17, 2016). Patients received first-line treatment with everolimus, 10 mg/d, plus letrozole, 2.5 mg/d. Second-line treatment with everolimus, 10 mg/d, plus exemestane, 25 mg/d, was offered at the investigator's discretion upon initial disease progression. The primary end point was investigator-assessed progression-free survival in the first-line setting per RECIST v1.0. Safety was assessed in patients who received at least 1 dose of study medication and at least 1 post-baseline safety assessment. A total of 202 women treated in the first-line setting had a median age of 64.0 years (interquartile range, 58.0-70.0 years) with metastatic (194 [96.0%]) or locally advanced (8 [4.0%]) breast cancer. Median progression-free survival was 22.0 months (95% CI, 18.1-25.1 months) with everolimus and letrozole. Median overall survival was not reached; 24-month estimated overall survival rate was 78.7% (95% CI, 72.1%-83.9%). Fifty patients started second-line treatment; median progression-free survival was 3.7 months (95% CI, 1.9-7.4 months). No new safety signals were observed. In the first-line setting, the most common all-grade adverse event was stomatitis (139 [68.8%]); the most common grade 3 to 4 adverse event was anaemia (21 [10.4%]). In the second-line setting, the most common adverse events were stomatitis and decreased weight (10 [20.0%] each); the most common grade 3 to 4 adverse event was hypertension (5 [10.0%]). There were 50 (24.8%) deaths overall during the study; 40 were due to study indication (breast cancer). The results of this trial add to the existing body of evidence suggesting that everolimus plus endocrine therapy is a good first-line treatment option for post-menopausal women with oestrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer (42) .

Discuss the potential risks from treatment with the pharmaceutical compared with current treatment options (if any).

Combination therapy was associated with a higher risk of adverse events than with exemestane alone, suggesting a need for careful benefit/risk assessment prior to treatment initiation. Most common AEs observed in the everolimus studies include stomatitis, rash, infection, non-infectious pneumonitis, and hyperglycaemia (9). Non-infectious pneumonitis is a class effect of rapamycin derivatives and can be severe and on rare occasions fatal. It has been reported in up to 19 % of everolimus recipients in clinical trials. A meta-analysis of five clinical trials (n=2233 patients, of whom 989 had breast cancer) showed that the incidence of all-grade and grade 3 or 4 pulmonary toxicity (i.e. pneumonitis) in everolimus 10 mg/day recipients was 10.4 and 2.4 %, respectively, and the risk of developing pulmonary toxicity of these grades was significantly ($p<0.001$) higher with everolimus than with control (placebo or active comparator) [RR 31.1; (95 % CI 8.9–109.6) and 8.8 (95 % CI 2.4–32.2), respectively]. It should be noted that the analysis could not assess the impact of smoking status or of other comorbidities (such as chronic broncho-pneumopathy or inflammatory lung disease) on pulmonary toxicity, as these data were not available in the primary trials (43). As earlier stated, treatment interruptions and/or dosage adjustments and other strategies may be required for the management of these adverse events (9).

Are there sub-populations that have higher potential benefits or risks? If so, please describe.

Highest potential benefits might be expected in patients who have developed resistance to existing treatments.

Would this treatment provide any health benefits or risks to any people beyond the individual who was receiving treatment? If so, what benefits or risks would result?

Benefits to others could involve improved quality of life for the patient being reflected in less stress and worry for family and whanau who are the primary carers.

How would funding the pharmaceutical result in other measurable benefits or risks to the health sector, eg changes in number of surgeries, hospitalisations, nursing time, diagnostic tests?

Such treatment is expected to delay or prevent need for chemotherapy.

Suitability

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications

Are there any features of the treatment that may impact on its use (eg method of delivery, size, shape, taste)? If so, please explain.

This is an oral treatment requiring 1 tablet daily.

Costs and savings

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications

Would the funding of this treatment create any costs or savings to the health system (eg would treatment require increased monitoring, or would it free up clinician time)?

Use of this treatment may delay or prevent the need for chemotherapy – which would free up resources.

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