Everolimus: finding its place in the treatment of hormone receptor-positive advanced breast cancer

Stephen RD Johnston*,[1]
& Belinda Yeo[1,2]
[1]Royal Marsden NHS Foundation Trust, Sutton, SM2 5PT, UK
[2]Institute of Cancer Research, Sutton, UK
*Author for correspondence:
Tel.: +44 207 808 2748
Fax: +44 207 808 2563
stephen.johnston@rmh.nhs.uk;

Therapy in practice

- Resistance to endocrine therapy in metastatic hormone receptor positive breast cancer is common.
- Targeted therapies, often in combination with endocrine agents, may help to overcome some of this resistance and delay or postpone chemotherapy.
- Everolimus, an mTOR inhibitor, is the first drug of its class to be licensed for use in postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer, in combination with exemestane.
- This combination treatment introduces potential new toxicities for breast cancer patients which require careful monitoring, early recognition and in some cases prophylaxis.

Despite the various treatment options for patients with advanced hormone receptor-positive breast cancer, progression on endocrine treatment remains a significant problem. Overactivation of certain molecular pathways, including the PI3K/Akt/mTOR pathway, may contribute to such resistance. Everolimus is an mTOR inhibitor that blocks signaling in this pathway and has been shown in clinical studies to improve progression-free survival in patients who have previously responded to endocrine treatment. It provides a new therapeutic option for patients in this setting, ideally prolonging their time to chemotherapy. Here, we discuss the rationale for its use in combination with endocrine therapy in advanced breast cancer. The challenges in using everolimus in this patient population include predicting which patients have the greatest likelihood of benefit, being mindful of its potential toxicities and determining the timing in which it is best introduced into treatment.

Keywords: breast cancer • endocrine resistance • everolimus • mTOR

Background

While death rates from breast cancer have fallen over the past three decades, it remains the second leading cause of cancer-related death in women [1]. Despite advances in early breast cancer management, approximately half of women diagnosed with early breast cancer will go on to develop advanced/metastatic disease [2].

Endocrine treatments in hormone receptor-positive advanced breast cancer

Most patients with metastatic breast cancer (MBC) are estrogen receptor (ER) positive and HER2 negative, and endocrine therapy is often the initial recommended first-line therapy for these women. Aromatase inhibitors (AIs) have shown significant clinical benefit over other endocrine thera-

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pies in advanced breast cancer [3,4], and hence they have become the first-line treatment of choice for ER-positive breast cancers in postmenopausal women who develop metastatic disease. There are two classes of third-generation AIs: the nonsteroidal aromatase inactivators (letrozole and anastrozole) and steroidal AIs (exemestane). Both classes are superior to tamoxifen in advanced breast cancer [4,5], although in clinical practice, letrozole or anastrozole are most commonly used as first-line treatments. Second- and third-line endocrine options tend to include using tamoxifen, if it has not been used previously, and alternative AIs, such as exemestane or the steroidal antiestrogen fulvestrant.

Fulvestrant is an ER downregulator with no agonist effects. It is administered by intramuscular injection monthly with a loading dose given during the first month of treatment at 2 weeks. In the EFECT Phase III randomized trial, 694 postmenopausal women with ER-positive MBC who had progressed after an AI were randomized to either 250 mg of fulvestrant or exemestane [6]. The objective tumor response rate was similar in both arms (7.4 vs 6.7%), as was the duration of clinical benefit that included patients with stable disease for at least 6 months (9.3 vs 8.3 months). Subsequently, the approved dose of fulvestrant is 500 mg monthly after a loading dose schedule, as identified in the CONFIRM study [7].

Similarly, in the SoFEA study, of the 693 patients who were preexposed to nonsteroidal AIs (predominantly in the metastatic setting), there was no significant difference in efficacy between fulvestrant (with or without combined estrogen deprivation by anastrozole) or exemestane [8],. Thus, at the time of progression on a nonsteroidal AI, further endocrine therapy alone has minimal efficacy, and better strategies are needed in order to understand and overcome endocrine resistance.

Endocrine resistance

There are two main types of endocrine resistance described in the published literature: primary or *de novo* resistance, in which no initial benefit has been seen with endocrine therapy; and secondary or acquired resistance, in which resistance develops over time following an initial response to endocrine therapy. The precise clinical definitions of endocrine-sensitive and -resistant disease often vary between trials, and this variation should be taken into account when directly comparing outcomes from trials. Similarly, there are numerous mechanisms of endocrine resistance [9], but increasingly, research has investigated changes in the PI3K/Akt/mTOR pathway as being very relevant in ER-positive breast cancer.

PI3K/Akt/mTOR pathway

Deregulation of this intracellular signaling pathway is a feature of many cancers [10] and is thought to play a key role in endocrine resistance in breast cancer. The central component of the pathway is the PI3K heterodimer [11]. The pathway is activated following transmembrane growth factor receptor tyrosine kinase activation, and subsequent phosphorylation of the receptor results in interaction with PI3K either directly or indirectly (Figure 1). Akt is a serine/threonine kinase that is the major effector of the pathway, and Akt signaling leads to increased intracellular growth and cell survival [12,13]. One important downstream consequence of PI3K/Akt activation is the alleviation of suppression by TSC1/2 of mTOR [14]. mTOR is serine/threonine kinase that regulates cell growth and proliferation via mTORC1 and mTORC2 [15].

The ER can become involved with the PI3K/Akt/mTOR pathway in breast cancer cells [16], with both genomic and nongenomic cross-talk occurring between this signaling pathway and ER [17]. Due to its role in cell survival, there is evidence that the PI3K/Akt/mTOR pathway becomes activated in acquired hormone-resistant breast cancer and accounts for the survival of cells despite the presence of continued endocrine blockade [18,19]. As such, preclinical data have confirmed the role of the PI3K/mTOR/Akt pathway in endocrine resistance in ER-positive breast cancer. In particular, targeting a downstream element of the pathway, such as mTOR, in combination with endocrine therapy (tamoxifen or an AI) has been shown to restore endocrine sensitivity in both cell lines and xenograft models [20,21], and thus provides a strong rationale for combining these therapies in the clinical setting of ER-positive advanced breast cancer in which endocrine resistance has developed.

Everolimus

Everolimus is potent oral mTOR inhibitor that has demonstrated antiproliferative activity against a wide variety of tumor models *in vivo* [22] and is a licensed treatment in other malignancies, such as renal cell cancer. It has subsequently been investigated in combination with endocrine therapy in endocrine-resistant, hormone-positive, HER2-negative advanced breast cancer, as described below.

Clinical trials of everolimus in MBC

To date, the two most important studies of everolimus in combination endocrine therapy for postmenopausal women with hormone receptor-positive MBC who have already received prior endocrine therapy are the TAMRAD Phase II study and the BOLERO-2 Phase III trial.

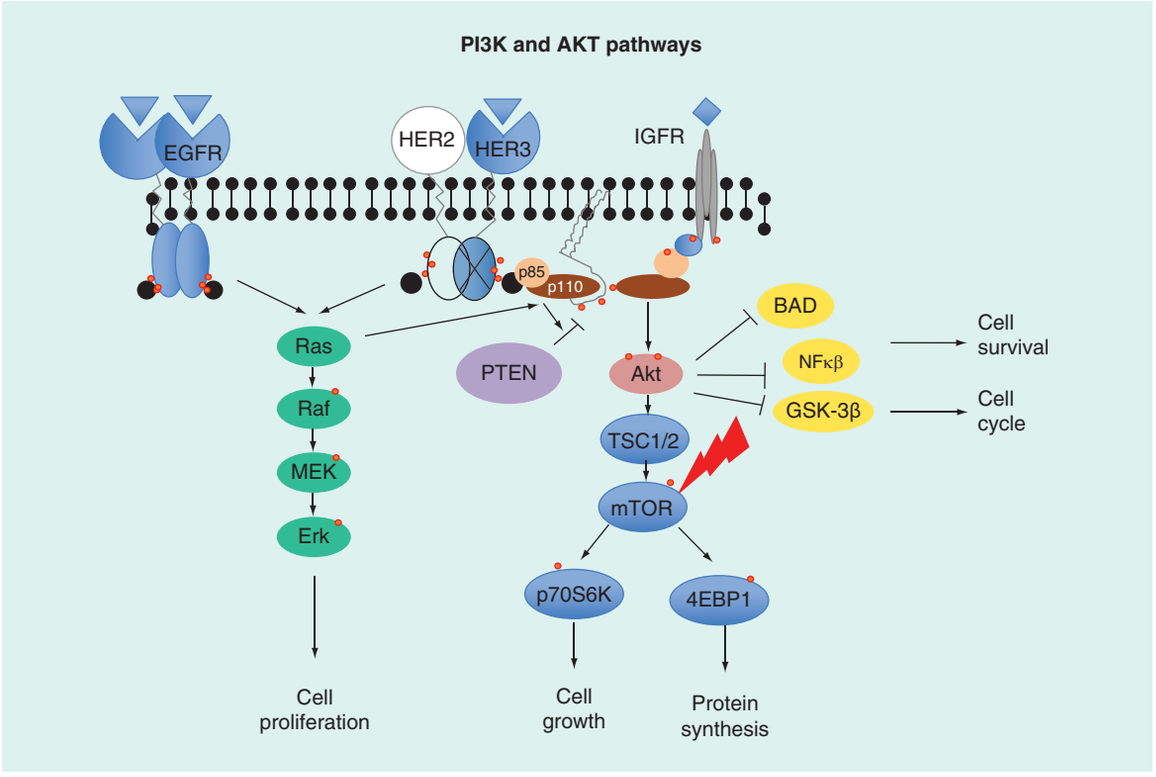

Figure 1. The PI3K/Akt/mTOR pathway.

TAMRAD: Phase II study

In the TAMRAD Phase II study, 111 postmenopausal patients with hormone receptor-positive breast cancer previously treated with an AI were randomized to tamoxifen and everolimus or tamoxifen alone [23]. The clinical benefit rate was the primary end point and favored the everolimus arm (61 vs 42%). The addition of everolimus significantly improved progression-free survival (PFS; 8.6 vs 4.5 months; p = 0.002). At the last published update, the median survival was 32.9 months in the tamoxifen arm and had not been reached in the combination arm [23].

Importantly, patients were stratified according to type of resistance shown to prior endocrine therapy – resistance was defined as relapse on or within 6 months of stopping adjuvant AI treatment or progression within 6 months of starting AI treatment in the metastatic setting. Alternatively, secondary resistance was defined as relapse more than 6 months since completion of an adjuvant AI treatment or relapse after more than 6 months on an AI in the metastatic setting (i.e., after some clinical benefit). An exploratory subgroup analysis suggested that the greatest clinical benefit from the combination arm occurred in patients with acquired or secondary resistance. Patients with secondary resistance gained more from everolimus, with a clinical benefit rate of 74 versus 48%, compared with only 46 versus 36% in primary resistance.

These clinical data support the hypothesis that tumors, which initially respond and then develop resistance to AIs, may overcome such resistance with mTOR inhibition, and that this combined approach should be most effective when used for those patients that progress during or after nonsteroidal AI therapy [24].

BOLERO-2: Phase III study

In the large BOLERO-2 Phase III randomized trial, 724 postmenopausal patients with advanced breast cancer who had recurrence of progression after an AI were randomized in a 2:1 ratio to exemestane combined with everolimus or placebo [25].

Patients were eligible if they had progressed on or within 12 months of their adjuvant AI treatment or during or following recent completion (within 1 month) of an AI treatment for advanced disease. In this trial, a nonsteroidal AI was the last line of treatment prior to study entry in 74% of patients. Just over half (56%) of the patients had visceral involvement, 68% had prior chemotherapy, 48% had prior tamoxifen and 16% had prior fulvestrant. More than 80% of patients in BOLERO-2 had received two or more lines of treatment for their advanced disease [25]. However, only a single line of chemotherapy in the metastatic setting was permitted.

The preliminary report showed that the median PFS more than doubled in the treatment combina-

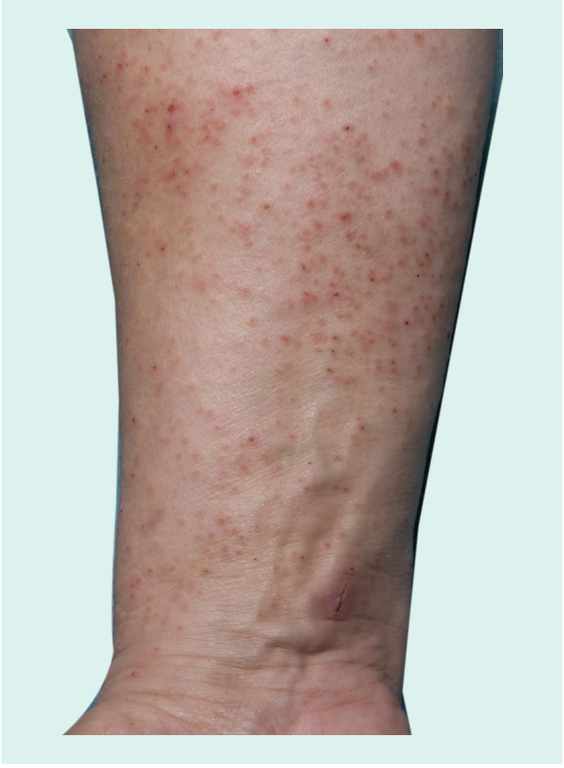

Figure 2. Rash appearing 1 month after commencing combination everolimus/exemestane treatment.
Everolimus was temporarily stopped and the patient was treated with topical emollients and antihistamines.

tion arm (10.6 vs 4.1 months favoring the everolimus/exemestane combination; hazard ratio [HR] 0.36 [25]). This was a very substantial improvement in PFS, the magnitude of which has never previously been seen in an endocrine study in MBC.

The subsequent 18-month follow-up data presented at the San Antonio Breast Cancer Symposium in December 2012 showed that PFS (as assessed by central review) was 11 months for everolimus plus exemestane versus 4.1 months for exemestane alone (HR: 0.38; $p < 0.0001$) [26]. Objective tumor response rates were 9.5% in the everolimus/exemestane arm versus only 0.4% in the exemestane-alone arm ($p = 0.001$). In the most recent update from BOLERO-2, the median duration on the everolimus/exemestane combination was nearly 6 months (23.9 weeks) [26]. Notably, 84% of patients were deemed to have had prior endocrine sensitivity, and as such, the trial mainly contained patients with acquired secondary resistance to AIs [26].

Biomarker analysis was successfully performed on 227 patient tissue samples in BOLERO-2 and presented recently [27]. The most frequently altered genes in this sample were *PIK3CA* mutations; cyclin D1, *P53* and *FGFR* were the most common, with *PIKC3A* mutations seen in 48%. An exploratory analysis examining the effects of these most common mutations showed no predictive marker of treatment response to everolimus and exemestane. Further validation of these results is planned. It should be noted that only 20% of these tissue samples came from metastatic sites and that mutation status may have changed from the primary tumor to the development of metastatic disease [27].

Safety & tolerability of everolimus

In both the TAMRAD and BOLERO-2 studies, there was an increased incidence of side effects seen in the everolimus arm. These included stomatitis, fatigue, rash, diarrhea, pneumonitis and hyperglycemia [23,25]. While most were grade 1 or 2 in severity, these are new toxicities to a population of patients familiar with the relatively mild toxicities from hormone treatment alone. In BOLERO-2, there was a relatively high discontinuation rate due to a lack of tolerance to combined treatment at 19% [25]. A total of 23% of patients in the everolimus arm had serious adverse advents, of which 11% were attributed to the treatment [25]. However, adverse events in BOLERO-2 were not any more frequent in patients over 65 years of age [28].

Everolimus: the first approved mTOR inhibitor to be licensed in breast cancer

Given the magnitude of benefit in the BOLERO-2 study, the US FDA approved everolimus for use in combination with exemestane for postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in 2012. At the same time, the EU approved everolimus for the same population of postmenopausal women without symptomatic visceral disease after recurrence or progression following a nonsteroidal AI, which is the currently approved licensed indication in the UK. The current cost to the healthcare provider for 1 month of treatment is approximately UK£3500 [29]. In the UK, the NICE are reviewing the data in order to determine the cost–effectiveness of this treatment. At present, funding for the treatment on the NHS is available through the Cancer Drugs Fund.

Other molecular inhibitors of the PI3K/Akt/mTOR pathway

While mTOR inhibitors are the most advanced that are currently in clinical study in breast cancer, other components of the PI3K/Akt/mTOR pathway have become potential therapeutic targets, including Akt inhibitors, isoform-specific PI3k inhibitors and, more recently, dual mTOR/PI3k inhibitors, which are being evaluated in Phase I and II clinical trials.

Place in therapy (insight & evidence from personal experiences of using the drug)

The efficacy of the combination of everolimus and exemestane in those patients who are refractory to prior AI therapy is a major advance in providing greater clinical benefit compared with simply further endocrine therapy alone, as shown previously in EFECT and SoFEA, with median PFS of only 3–4 months. Importantly, this combination may spare the use of palliative chemotherapy for a period of time. However, it is unclear whether the same magnitude of improvement will be seen in the first-line endocrine-sensitive population, for whom the median PFS to AI therapy can be 9–15 months. The only study to address this with mTOR inhibitors has been with the oral mTOR antagonist temsirolimus.

Having previously shown efficacy in the intravenous preparation [30], the Phase III HORIZON trial randomized over 1112 MBC patients to oral temsirolimus (30 mg orally for 5 days every 2 weeks) in combination with letrozole or letrozole/placebo [31]. This trial was closed early due to futility, with no improvement seen in PFS (median: 9 months; HR: 0.90; p = 0.25). The key difference in this study compared with those mentioned above was that the study population had not received prior hormonal therapy for their advanced disease. These data suggest that selecting those patients with acquired or secondary resistance is most important in terms of deriving benefit from mTOR-targeted therapies, and that first-line therapy of the combination may not be any better than an AI alone.

Patient selection

Thus, from the data available that have been described in the above trials, response to everolimus appears to hinge on prior endocrine responsiveness and the subsequent development of endocrine resistance. BOLERO-2 was predominantly a study in patients with prior endocrine-responsive disease, with 84% of patients having had previous sensitivity to endocrine therapy [25]. However, in this trial, benefit was seen in both groups of patients, including those with *de novo* resistance. In the TAMRAD trial, those with acquired secondary resistance derived the most clinical benefit [23]. Hence, patients who have demonstrated response to endocrine therapy in the metastatic setting – particularly an AI (but also tamoxifen and/or fulvestrant) – and subsequently progressed should be identified as potential candidates for therapy. Alternatively, those with primary resistance are less likely to respond based on the currently available evidence, and alternative therapy may be required.

While everolimus has been used in other cancer settings, such as advanced renal cell carcinoma and pancreatic neuroendocrine tumors, it is a relatively new therapy to the breast cancer clinician. There is wide variation in the extent to which patients with MBC are affected by their disease. There are a significant proportion of patients who remain largely asymptomatic from their secondary disease for many years, which is perhaps in contrast to other patient populations taking everolimus in other cancer settings. A patient with asymptomatic bone metastases, for example, may have had many months or even years of remission on hormone therapy, with potentially few if any side effects from treatment. Given the potential side effects mention above, a history of underlying lung disease, diabetes and dyslipidemia prior to the commencement of treatment should be documented, and monitoring for the symptoms and signs of any exacerbations is critical.

Timing & sequencing of treatment in MBC

It is possible to consider everolimus in our repertoire of therapy as a chemotherapy-sparing or -postponing maneuver. This would most likely be in the setting of low burden or minimally symptomatic visceral disease. It may also be considered after chemotherapy when residual the disease burden is low. However, once again, we must emphasize that prior sustained benefit from an AI for advanced disease may be an important prerequisite in our opinion. In BOLERO-2, only a single line of chemotherapy for advanced disease was permitted to entry into study. Hence, we have no evidence for the everolimus/exemestane combination as a salvage therapy after multiple lines of chemotherapy. Thus, while it is tempting to use everolimus in patients who are heavily pretreated, evidence for sustained benefit in this setting is limited.

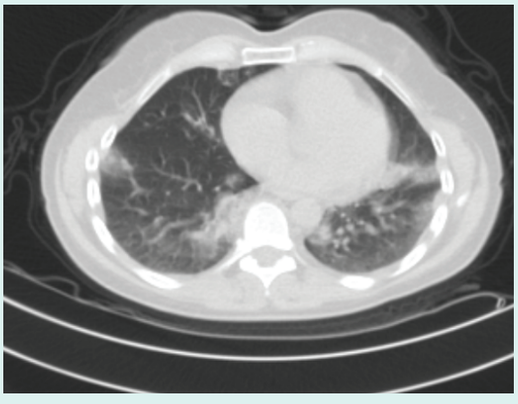

Figure 3. Asymptomatic patient after 3 months of everolimus/exemestane who developed hypermetabolic air space and ground-glass opacities on PET–CT scan bilaterally, predominantly involving the lower lobes.

How to manage toxicity

The benefits of mTOR-targeted therapy need to be considered in light of their potential and not insignificant toxicities, particularly given patients who are considered appropriate for such treatment may be doing so in order to avoid or postpone the need for chemotherapy and its associated toxicities. Educating patients as to the potential side effects of treatment is vital for detecting toxicity, with specific attention being paid to stomatitis, rash, respiratory symptoms and hyperglycemia. Close monitoring in the initial weeks of treatment (at 2 and 4 weeks) after starting therapy is advised in order to monitor for rash, stomatitis or a dry cough, although these toxicities may also occur in subsequent cycles. Toxicity can resolve with time, but dose interruption or dose delay may be required.

Prior to the commencement of treatment, a history of underlying lung disease, diabetes and dyslipidemia should be documented, and monitoring for symptoms or signs of any exacerbations is critical. Stomatitis mimics apthous stomatitis [32] and is usually of rapid onset. Patients may be administered mouth washes prophylactically at the time of commencing this drug combination. In the setting of grade 2 or higher symptoms, treatment should be interrupted until it resolves to grade 1 and a dose reduction may be necessary. Rash associated with mTOR inhibitors can be severe, requiring dose interruption, reduction or cessation (Figure 2). Topical emollients, topical steroids and topical antibiotic preparations such as clindamycin may be required. Mild diarrhea may be managed with symptomatic treatments such as loperamide, but if it becomes more severe, then withholding treatment may be necessary. Elevation of blood glucose and lipid levels may occur early during treatment initiation and should be monitored regularly. With the development of new, persistent hyperglycemia, treatment cessation may be necessary and treatments such as oral hypoglycemic agents may be required. Mild elevations of lipids may be appropriately managed with lifestyle modifications; however, more severe dyslipidemia may require treatment interruption or cessation and statin therapy.

The pathogenic mechanism of everolimus noninfectious pneumonitis is not fully understood but is thought to be immune mediated (Figure 3). Particular emphasis on identifying the signs of pneumonitis, such as cough and dyspnea, should alert the patient to present for clinical review. Pneumonitis may be graded according to severity. In the metastatic renal cell carcinoma literature, grade 1 pneumonitis is defined as asymptomatic changes in imaging, and the drug may be continued with close monitoring. Grade 2/3 pneumonitis suggests temporary cessation and possible oral steroids; grade 4 pneumonitis suggests permanent discontinuation [33]. It is at the clinician's discretion whether a rechallenge is reasonable.

Dosing & administration

The recommended dose of everolimus is 10 mg orally daily in combination with exemestane 25 mg orally daily. In BOLERO-2, dose reductions were permitted that included an initial reduction to 5 mg daily followed by a subsequent reduction to 5 mg on alternate days. Reasons for dose reductions would include grade 2/3 toxicity on full-dose everolimus that resolved to grade 1 or completely prior to its reintroduction.

Therapy in practice

The patient case is a 68-year-old woman with metastatic breast cancer under consideration for everolimus/exemestane. The original diagnosis of right breast cancer occurred at 48 years of age. The treatment of this breast cancer involved wide local excision, node-negative axilla and adjuvant radiotherapy and tamoxifen. Thirteen years after the original breast cancer diagnosis, the patient developed metastatic disease with

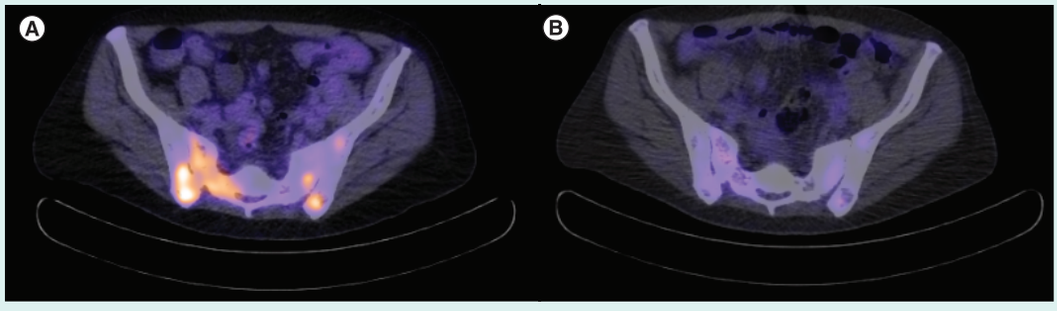

Figure 4. PET response in bone after 3 months of combination everolimus/exemestane therapy.

hilar lymphadenopathy, right chest wall mass and bone metastases. Biopsy confirmed grade 2, estrogen receptor-positive metastatic breast cancer. The treatment for this involved letrozole and bisphosphonate therapy. Two years later, asymptomatic progression occurred, with a rise in tumor markers. The treatment for this involved a change to exemestane. Six months later, progression with new asymptomatic liver metastases and progression in the bone occurred. The treatment for this involved a switch to oral capecitabine. Two years later, there was progression in bone disease (68 years of age). The treatment for this involved a switch to everolimus and exemestane. After 3 months of everolimus and exemestane, response in the bone was observed on PET scan, and treatment continued (Figure 4).

In this case, this patient has shown prior endocrine sensitivity with more recently visceral and bone metastases. She responded to the everolimus/exemestane combination after one prior line of chemotherapy for metastatic disease.

Conclusion

Targeted inhibition of the mTOR pathway with drugs such as everolimus provides a promising new strategy for the treatment of hormone-resistant MBC. From the published Phase III BOLERO-2 data, everolimus in combination with exemestane significantly improves PFS in patients who have previously been exposed to AIs. In our opinion, it is important when using everolimus to consider the patient's prior response to endocrine therapy, targeting those patients with secondary or acquired resistance to prior endocrine therapy. The toxicity profile, with particular reference to rash, stomatitis and pneumonitis, needs to remain at the forefront of the clinician's mind when monitoring these patients for treatment optimization.

Future perspective: future studies of everolimus in breast cancer

There are several studies currently underway investigating the potential role of everolimus in HER2-positive and triple-negative breast cancer, as well as in combination with chemotherapy. A randomized Phase III trial (BOLERO-1) of everolimus in combination with trastuzumab and paclitaxel as a first-line therapy in women with HER2-positive advanced breast cancer has enrolled 719 patients and is due to report soon. Data from the BOLERO-3 study of 569 postmenopausal women with HER2-positive advanced breast cancer who received prior taxane therapy and experienced recurrence or progression on trastuzumab were recently presented [34]. Patients were randomized to receive either everolimus (5 mg daily) or placebo in combination with weekly trastuzumab and vinorelbine (25 mg/m^2). There was only a modest improvement in PFS favoring the everolimus arm (7 vs 5.78 months; HR: 0.78; p = 0.0067) [34].

The role of everolimus in the first-line setting in ER-positive MBC remains unclear. Trials currently recruiting include a Phase II study (BOLERO-4) of everolimus plus letrozole in the first-line treatment of ER-positive MBC (NCT01698918) and a three-arm Phase II study (BOLERO-6) of everolimus and exemestane versus everolimus alone versus capecitabine in patients after failure of nonsteroidal AI therapy (NCT01783444).

Everolimus is the first drug in this class of agents to be licensed in MBC. However, several other targets within the PI3K/Akt/mTOR pathway have been identified and are currently being evaluated in clinic trials, including inhibition of TORC1, PIC3CA, Akt and various dual-targeted agents.

There are also several studies of everolimus combined with endocrine therapy proposed in the adjuvant setting, either in higher-risk, HR-positive postmenopausal women (SWOG-NSABP S1207; NCT01674140) or in a randomized switch after 2 years of adjuvant endocrine therapy (UNICANCER; NCT01805271).

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