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The Role of Everolimus in the Treatment of Breast Cancer

José Pablo Leone[1], Ricardo H. Álvarez[2*]

[1]University of Pittsburgh Cancer Institute, Pittsburgh, USA; [2]Department of Breast Medical Oncology, Morgan Welch Inflammatory Breast Cancer Research Program and Clinic, University of Texas, M. D. Anderson Cancer Center, Houston, USA.
Email: *ralvarez@mdanderson.org

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ABSTRACT

The development of resistance to chemotherapy, endocrine therapy and anti HER2 agents in breast cancer is an important and common problem that impacts in the management of patients, particularly in the metastatic setting. This resistance has been explained in part by the activation of signal transduction pathways, including the PI3K/AKT/mTOR. The blockade with mTOR inhibitors such as everolimus is a new target agent for therapy that attempts to enhance treatment efficacy and restore tumor sensitivity. In this review article, we present the data about the use of everolimus for the treatment of breast cancer in all tumor phenotypes. Future studies that evaluate biomarkers for treatment response are needed to identify the specific populations that have the highest benefit of this new targeted therapy.

Keywords: Advanced Breast Cancer; Everolimus; mTOR Inhibitors

1. Introduction

Breast cancer continues to be a very prevalent disease worldwide. In 2011, it is estimated that more than 39,000 women died of breast cancer in the United States [1].

Advances in the treatment of early-stage including screening programs for breast cancer detection and adjuvant systemic treatments for breast cancer have improved outcomes for patients. Despite these improvements, however, many women ultimately develop metastatic breast cancer (MBC), which is essentially an incurable disease. The prognosis of patients with MBC has changed little over the past decade; the majority of patients succumb to their disease within 2 years of diagnosis [2-4]. Intrinsic or acquired resistance to chemotherapy, endocrine therapy and anti-HER2 agents is in part responsible for the poor outcome of these patients [5]. New and novel treatments for patients with breast cancer are needed to avoid the development of metastatic disease and improve survival of patients with MBC, while minimizing toxicity.

2. Biology of the PI3K/AKT/mTOR Pathway

The mammalian target of rapamycin (mTOR) is a serine-threonine protein kinase that regulates cell metabolism, proliferation, survival, migration and apoptosis [6-8]. The mTOR belongs to the phosphatidylinositol triphosphate-kinase (PI3K)-protein kinase B (AKT) signaling pathway (**Figure 1**) [6,9]. This pathway promotes translational changes through several downstream cascades [8,10]. It is activated when a growth factor binds to its tyrosine kinase receptor such as the insulin like growth factor 1 receptor or the human epidermal growth factor receptor (HER). PI3K in turn activates AKT by phosphorilation and AKT regulates mTOR which is involved in the final part of the signaling.

Dysregulation of this pathway, specifically upregulation of mTOR, has been associated with many types of cancer, including breast cancer [7]. Along with the upregulation of mTOR, there is also over expression of the growth factor receptor and loss of phosphatase and tensin homolog (PTEN), which is a tumor suppressor gene and an inhibitor of the mTOR pathway [6]. These mechanisms promote cell proliferation and survival [10].

Breast cancer has been associated with mutations in the PI3K gene and PTEN loss of function [11]. The latter has also been shown to be a marker of poor prognosis in patients with estrogen receptor (ER) positive breast cancer treated with tamoxifen [12].

The activation of the PI3K/AKT/mTOR pathway has a role in the development of resistance to chemotherapy, endocrine therapy and anti-HER2 agents [10,13-17]. This novel concept prompted the use of mTOR inhibitors in

*Corresponding author.

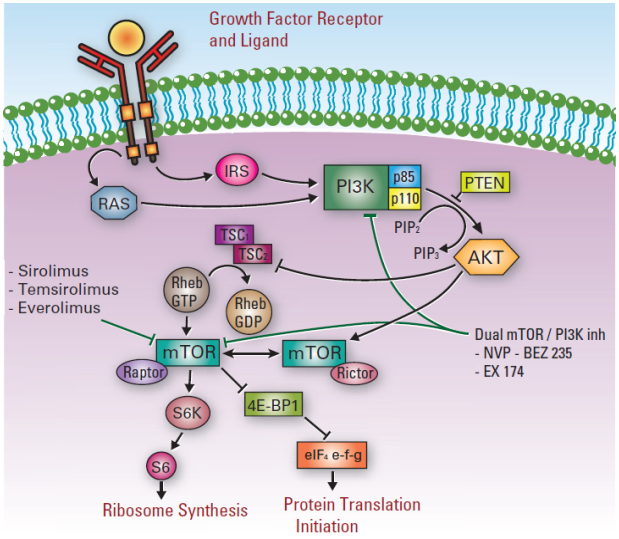

Figure 1. The mammalian target of rapamycin (mTOR) signal network. mTOR is a highly conserved pathway that regulates cell proliferation and metabolism in response to environmental factors. The growth factor receptor is linked with mTOR signaling via the phosphatidylinositol-3-kinase (PI3K)/Akt family. PTEN plays an important role in this pathway; loss of PTEN function through mutation, deletion, or epigenetic silencing results in increased activation of Akt and mTOR. The mTOR proteins regulate activities of the translational regulators 4E-BP1 and p70S6 kinase (S6K). mTOR antagonists have been developed to inhibit mTORC1 (raptor).

combination with the above mentioned therapies in an attempt to enhance efficacy and reverse tumor resistance.

3. Everolimus

Finding the most appropriate mTOR agent to use in the management of breast cancer has been a topic of recent extensive research. Everolimus derivate of sirolimus and is a strong oral mTOR inhibitor. It inhibits mTOR by binding to the FK506 binding protein 12 (FKBP-12) and phosphorylating one of the mTOR substrates, the P70 S6 ribosomal protein kinase. This complex inhibits protein synthesis and cell proliferation. It also blocks angiogenesis by decreasing the activity of vascular endothelial growth factor (VEGF) [18].

Everolimus has a rapid but moderate absorption through the gastrointestinal tract with peak concentrations after 1 to 3 hours and a bioavailability of 30%. It is 74% protein bound and is metabolized in the liver via CYP3A4 and P-glycoprotein. The excretion is mainly fecal with a half life of 30 hours [19].

Currently, everolimus has been approved by the Food Drug Administration (FDA) for the use in patients with unresectable pancreatic neuroendocrine, metastatic renal cell carcinoma after failure to sunitinib or sorafenib, and also was FDA granted for the treatment of angiomyolipoma, tuberous sclerosis and subependymal giant cell astrocytoma. Most recently, everolimus was approved in combination with exemestane for the treatment of postmenopausal patients with metastatic breast cancer that progressed to treatment with anastrozole or letrozole.

The initial studies with mTOR inhibitors as single agent in patients with solid tumors demonstrated a clinical benefit in less than 10% of the patients [20]. A larger phase I study showed benefit in 17% of patients of which almost a third had renal cell cancer [21].

The use of mTORs inhibitors in breast cancer in combination with anti-hormone agents demonstrated some confounding data. A phase III study evaluating temsirolimus in addition to letrozole in locally advanced or metastatic breast cancer showed no improvement in progression free survival (PFS) or objective response rate (ORR) [22]. Everolimus, however, on a phase II study combined with tamoxifen demonstrated increased clinical benefit, PFS and overall survival (OS) [23].

4. Everolimus in Combination with Endocrine Therapy

Endocrine therapy has been a very effective treatment in patients with ER positive tumors; however resistance to this therapy in the metastatic setting is a relevant problem. One of the mechanisms of resistance is related to the PI3K/AKT/mTOR pathway activation, and therefore everolimus has been proposed to restore sensitivity. **Table 1** summarizes multiple phase I-III studies of everolimus with endocrine therapy in the setting of ER positive metastatic breast cancer.

A phase I study evaluated everolimus 5 or 10 mg daily in addition to letrozole 2.5 mg daily. A total of 18 patients were evaluated, one had a complete response that lasted 22 months and another patient had a 28% reduction of liver metastases [24].

In a large randomized, double-blinded, phase II study, 270 postmenopausal women with palpable (>2 cm) ER positive tumors were treated with neoadjuvant letrozole with or without everolimus. Patients were treated for 16 weeks and biopsies were performed at baseline and at day 15 for biomarker assessment. The primary endpoint was response rate by clinical palpation, which was significantly higher in the everolimus arm (68.1% vs 59.1%, $p = 0.062$). Significant reductions in progesterone recaptor and cyclin D1 occurred in both treatment groups, and large downregulation of phospho-S6 occurred only in the everolimus arm. An antiproliferative response with reduction in Ki67 occurred more frequently in the everolimus group (57% vs 30%, $p < 0.01$) [25].

The Tamoxifen-RAD001 (TAMRAD) study was an open-label, phase II, randomized study that evaluated tamoxifen in combination with everolimus in patients with hormone receptor positive, HER2 negative metastatic

Table 1. Clinical studies evaluating the use of everolimus in patients with HR-positive breast cancer.

Study	Design	n	Patient characteristics	Treatment	Endpoint	Results
Awada *et al.* [24]	Phase I	18	ER+, metastatic, stable or progressing after 4 or more months of letrozole.	everolimus 5 or 10 mg daily with letrozole 2.5 mg daily	Toxicity, efficacy	CR: 6% SD: 50%
Baselga *et al.* [25]	Randomized, double-blinded, phase II	270	ER+, postmenopausal, >2 cm, untreated.	Neoadjuvant everolimus 10 mg/day with letrozole 2.5 mg/day vs neoadjuvant placebo with letrozole 2.5 mg/day	RR by clinical palpation.	RR by clinical palpation: 68.1% vs 59.1%. RR by ultrasound: 58% vs 47%
Bachelot *et al.* [23]	Randomized, open-label, phase II	111	HR+, HER2−, postmenopausal, metastatic, previously treated with AI.	Tamoxifen 20 mg/day with everolimus 10 mg/day vs Tamoxifen 20 mg/day	CBR at 6 months	CBR: 61% vs 42% PFS: 8.6 months vs 4.5 months
Badin *et al.* [26]	Ongoing phase II	11	ER+, metastatic, progressed to AI within 6 months.	everolimus 10 mg daily with intramuscular fulvestrant 500 mg on day 1, 250 mg on days 14 and 28, and 250 mg monthly thereafter	PFS CBR for 24 weeks or longer	PFS: 8.6 months CBR: 55%
Baselga *et al.* [27]	Randomized, double-blinded, phase III	724	ER+, HER2−, postmenopausal, advanced breast cancer, refractory to anastrozole or letrozole.	exemestane 25 mg daily with placebo vs exemestane 25 mg daily with everolimus 10 mg daily	PFS (locally and centrally reviewed)	PFS by central review: 10.6 months vs 4.1 months PFS by local review: 6.9 months vs 2.8 months

AI: aromatase inhibitors; CBR: clinical benefit rate; CR: complete response; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; PFS: progression free survival; RR: response rate; SD: stable disease

breast cancer previously treated with aromatase inhibitors. The investigators randomized 111 patients to receive tamoxifen 20 mg daily alone or tamoxifen 20 mg daily with everolimus 10 mg daily. The primary endpoint was clinical benefit rate (CBR), defined as the percentage of patients with CR or PR or stable disease at 6 months. CBR was observed in 61% (95% CI 47% - 74%) in the combination group compared with 42% (95% CI 29% - 56%) in the tamoxifen alone group (exploratory p = 0.045). The combination group also had significantly longer PFS (8.6 mo vs 4.5 mo, p = 0.002) and superior OS with a hazard ratio (HR) of 0.45 (95% CI 0.24 - 0.81, exploratory p = 0.007). Interestingly, in an exploratory subgroup analysis, the authors found that the everolimus benefit was mostly for patients with secondary hormone resistance, with a reduction in the risk of progression associated with everolimus of 54% in this subgroup (HR, 0.46; 95% CI, 0.26 to 0.83), which favors the proposed mechanism of reversing endocrine resistance [23].

An ongoing phase II study of patients with ER positive metastatic breast cancer who failed aromatase inhibitor therapy within 6 months, is evaluating everolimus 10 mg daily in combination with intramuscular fulvestrant 500 mg on day 1250 mg on day 14,250 mg on day 28, and 250 mg monthly thereafter. The primary endpoint is PFS, and the secondary endpoints are toxicity, biomarker evaluation, ORR, and clinical benefit rate (CR + PR + stable disease for 24 weeks or longer). Preliminary results with only 11 patients enrolled showed a median PFS of 8.6 months and a clinical benefit rate of 55% [26].

The Breast Cancer trial of Oral Everolimus 2 (BOLERO-2) was a phase III randomized study evaluating everolimus with exemestane in patients with ER positive HER2 negative advanced breast cancer that is refractory to anastrozole or letrozole. A total of 724 patients were randomized 2:1 to receive exemestane 25 mg daily with placebo or exemestane 25 mg daily with everolimus 10 mg daily. The primary endpoint was PFS which was assessed separately by local investigators and central assessment. The median PFS by central review was 10.6

months with everolimus and exemestane and 4.1 months with placebo and exemestane (hazard ratio, 0.36; 95% CI, 0.27 to 0.47; $p < 0.001$). The ORR was superior in the everolimus arm (9.5% vs 0.4% $p < 0.001$). Survival data showed only 83 deaths which represented 10.7% in the everolimus arm vs 13% in the control group [27]. Due to the results of this study, the FDA approved the use of everolimus combined with exemestane on July 20, 2012 for postmenopausal women with metastatic breast cancer that had progressed to anastrozole or letrozole.

5. HER2 Positive Disease

Amplification or overexpression of the HER2 gene is found in around 15% - 20% of breast cancers [28]. Standard treatments in the adjuvant setting include the utilization of trastuzumab-containing regimens for up to 1 year [29]. Most recently, the novel agent pertuzumab was approved for the use in the metastatic setting in combination with docetaxel and trastuzumab [30].

A number of phase I and II studies have been conducted evaluating the efficacy of everolimus in patients with HER2-positive metastatic breast cancer. Their results are summarized in **Table 2**.

A phase Ib study evaluated 33 patients with metastatic breast cancer pretreated with trastuzumab who received everolimus 5 mg daily, 10 mg daily or 30 mg per week in combination with paclitaxel 80 mg/m^2 on days 1, 8 and 15 every 4 weeks and trastuzumab 2 mg/kg weekly. There were 27 patients with measurable disease that were evaluated for efficacy, of which 44% had ORR. The median PFS was 34 weeks, two patients had CR, 10 patients had PR and 13 patients had stable disease [31].

Subsequently, a follow-up phase II study was performed on patients with metastatic disease resistant to taxanes and trastuzumab [32]. Patients were treated with everolimus 10 mg daily and paclitaxel and trastuzumab in similar doses to the phase Ib study previously mentioned. From a total of 48 evaluable patients, 9 (19%) had PR and 30 (62%) had stable disease. The median PFS was 26 weeks.

Table 2. Clinical studies evaluating the use of everolimus in patients with HER2-positive breast cancer.

Study	Design	n	Patient characteristics	Treatment	Endpoint	Results
Andre *et al.* [31]	Phase Ib	33	HER2+, metastatic, pretreated with trastuzumab	everolimus 5 mg daily, 10 mg daily or 30 mg per week with paclitaxel 80 mg/m^2 on days 1, 8 and 15 every 4 weeks and trastuzumab 2 mg/kg weekly	Toxicity, efficacy	17 patients had grade 3 - 4 neutropenia. ORR: 44% PFS: 34 weeks.
Jerusalem *et al.* [33]	Phase Ib	50	HER2+, metastatic, progressed after trastuzumab	everolimus 5 mg daily, 20 mg weekly or 30 mg weekly with trastuzumab 2 mg/kg weekly and vinorelbine 25 mg/m^2 on days 1 and 8 every 3 weeks	Toxicity, efficacy	14 patients had grade 3 - 4 neutropenia. ORR: 19.1% CBR: 54% PFS: 30.7 weeks.
Morrow *et al.* [36]	Phase I/II	47	HER2+, metastatic, progressed after trastuzumab	Trastuzumab 6 mg/kg every 3 weeks with everolimus 5 or 10 mg daily	Toxicity, efficacy	PR: 15% SD: 19% PFS: 4.1 months
Dalenc *et al.* [32]	Phase II	48	HER2+, metastatic, resistant to taxanes and trastuzumab.	everolimus 10 mg daily with paclitaxel 80 mg/m^2 on days 1, 8 and 15 every 4 weeks and trastuzumab 2 mg/kg weekly	Efficacy	PR: 19% SD: 62% PD: 19% PFS: 26 weeks.

CBR: clinical benefit rate; HER2: human epidermal growth factor receptor 2; ORR: overall response rate; PFS: progression free survival; PD: progression of disease; PR: partial response; SD: stable disease.

Another phase Ib study evaluated everolimus daily or weekly in patients with HER2 positive metastatic breast cancer who progressed after trastuzumab. Patients were administered everolimus 5 mg daily, 20 mg weekly or 30mg weekly in combination with trastuzumab 2 mg/kg weekly and vinorelbine 25 mg/m^2 on days 1 and 8 every 3 weeks [33]. Median PFS was 30.7 weeks. A total of 47 patients were evaluated of which 19% had objective response and 54% had clinical benefit (CR + PR + stable disease for at least 24 weeks). The study had an extension phase in which patients were allowed to continue everolimus whereas vinorelbine could be stopped at the investigator's discretion [34]. Two patients had CR, one had PR and the median PFS was 41 weeks.

With the information from the above mentioned studies, a pooled analysis was conducted to assess the efficacy of everolimus in patients previously treated with lapatinib. A total of 101 patients were evaluated with an ORR of 21% for patients who received lapatinib compared with 29% for those that did not receive lapatinib [35]. The disease control rate was 88% and 81% respectively. The mean PFS was 29 and 36.1 weeks respectively. This study showed that everolimus combined with trastuzumab and chemotherapy was still efficacious even in patients pretreated with lapatinib, which formulated the possible role of everolimus in the reversal of resistance to anti-HER2 agents.

Trastuzumab resistance has been linked to activation of the PI3K/AKT/mTOR pathway. For this reason, a phase I/II study was conducted on patients with metastatic breast cancer who had progressed to trastuzumab [36]. This was a pooled analysis of 47 patients from two concurrent trials, patient received trastuzumab 6 mg/kg every 3 weeks in combination with everolimus 5 or 10 mg daily. The median PFS was 4.1 months. PR was seen in 7 patients (15%) and stable disease in 9 patients (19%). Interestingly, patients with PTEN loss demonstrated decreased overall survival ($p = 0.048$). However, PFS was not affected by PTEN loss.

6. Everolimus with Chemotherapy

Several studies have been conducted in patients with tumors that are HER2 negative, ER negative or triple negative (ER negative, PR negative, HER2 negative). These studies used the combination of everolimus with chemotherapy.

In an open-label phase Ib study, everolimus in three dose escalation levels (20, 25, and 30 mg/wk) was given with cisplatin 25 mg/m^2 and paclitaxel 80 mg/m^2 weekly for 3 weeks of a 4 weeks cycle. A total of 18 patients were evaluated, one had CR. PR and SD were seen in 5 and 9 patients respectively. Three patients progressed. The median PFS was 6 months [37].

A randomized phase II study evaluated patients with early stage or locally advanced triple negative breast cancer [38]. Patients were treated with neoadjuvant weekly paclitaxel 80 mg/m^2 alone or in combination with everolimus 30 mg weekly for 12 weeks followed by 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 4 cycles. A total of 50 patients were randomized. The 12 week response rate by ultrasound was 29.6% in the comparison group vs 47.8% in the experimental arm ($p = 0.15$). There was no significant difference between pathologic CR rates between the 2 groups. The therapy was well tolerated and further studies should be conducted to continue exploring this option in this high risk subset of patients.

7. Future Perspectives

Multiple studies are currently evaluating the combination of everolimus with chemotherapy and targeted-therapy for breast cancer. **Table 3** summarizes these trials. The research spectrum is very broad and embraces all settings from neoadjuvant to metastatic, however many of the studies are having difficulties with patient recruitment. The research questions that these studies intend to address are of significant relevance to the clinical practice and therefore enrollment should be emphasized to all patients.

8. Conclusions

The inhibition of the mTOR pathway is a new and excit ing option for the treatment of patients with breast cancer. The results of the clinical studies we discussed are very encouraging. In metastatic ER-positive breast cancer there is now a potential role for the combination of everolimus with steroidal aromatase inhibitors (AI) in patients previously exposed to non-steroidal AI. The National Comprehensive Cancer Network (NCCN) guidelines support this strategy for patients with endocrine therapy resistant breast cancer. The improvement of the PFS is associated with more toxicity and the cost increase of the regimen. There are at least two ongoing Phase III studies using everolimus in the adjuvant setting.

In patients with HER2-positive disease, results from early clinical data on combination with everolimus plus anti-HER2 therapies are encouraging. However, the results from larger studies are not available yet.

Although these are promising results, many patients still do not respond to these therapies. Important questions remain unanswered. Are there specific subgroups who receive greater benefit from everolimus? Is there a relationship between PIK3CA mutation and efficacy? Further studies with the inclusion of biomarker analysis for treatment response are needed to identify the subgroup of patients that benefit the most from the blockade of the mTOR pathway.

Table 3. Clinical studies evaluating the use of everolimus in combination with targeted therapy in advanced breast cancer.

Trial ID/Phase	Sponsor	Title	Regimen	Endpoint	Estimated enrollment
NCT01743560 Phase IV	Novartis Pharmaceuticals	A Phase IV Multicentre, Open Label Study of Postmenopausal Women with Oestrogen Receptor Positive Locally Advanced or Metastatic Breast Cancer Treated with Everolimus (RAD001) in Combination with Exemestane, with Exploratory Epigenetic Marker Analysis	Everolimus 10 mg daily and exemestane 25 mg daily	ORR PFS OS QOL	50 Not yet open
NCT01272141 Phase II	Emory University	Phase II Trial of Lapatinib in Combination with Everolimus in Triple Negative Metastatic or Locally Advanced Breast Cancer	Lapatinib 1250 mg daily and everolimus 5 mg daily	ORR Safety and toxicity	43 Recruiting
NCT00915603 Phase II	Sarah Cannon Research Institute	A Randomized, Double-Blind, Placebo-Controlled Phase II Trial of Weekly Paclitaxel/Bevacizumab +/− Everolimus as First-Line Chemotherapy for Patients with HER2-Negative Metastatic Breast Cancer (MBC)	Everolimus 10 mg daily + Bevacizumab 10 mg/kg Days 1 and 15 + Paclitaxel 90 mg/m^2 Days 1, 8, 15 vs Placebo + Bevacizumab 10 mg/kg Days 1 and15 + Paclitaxel 90 mg/m^2 Days 1, 8, 15	PFS Safety RR Duration of response OS	110 Not recruiting
NCT01520103 Phase II	AIO-Studien-gGmbH	Randomized Phase II Study to Compare Vinorelbine In Combination With the mTOR Inhibitor Everolimus vs. Vinorelbin Monotherapy for Second-line Treatment in Advanced Breast Cancer	Vinorelbine 25 mg/m² days 1, 8, 15 with or without Everolimus 5 mg daily	PFS Safety OS RR	166 Recruiting
NCT01305941 Phase II	UNC Lineberger Comprehensive Cancer Center	A Phase II Study Evaluating the Efficacy and Tolerability of Everolimus (RAD001) In Combination with Trastuzumab and Vinorelbine in the Treatment of Progressive HER2-Positive Breast Cancer Brain Metastases	Everolimus 5 mg daily + vinorelbine 25 mg/m^2 weekly + trastuzumab 2 mg/kg weekly	Intracranial RR Extracranial RR Toxicity	35 Recruiting
NCT01626222 Phase III	Novartis Pharmaceuticals	A Phase IIIB, Multi-Center, Open Label Study for Postmenopausal Women With Estrogen Receptor Positive Locally Advanced or Metastatic Breast Cancer Treated with Everolimus (RAD001) in Combination with Exemestane: 4EVER-Efficacy, Safety, Health Economics, Translational Research	Everolimus 10 mg daily and exemestane 25 mg daily	ORR PFS OS Safety QOL	300 Recruiting
NCT00876395 Phase III	Novartis Pharmaceuticals	A Randomized Phase III, Double-Blind, Placebo-Controlled Multicenter Trial of Everolimus in Combination with Trastuzumab and Paclitaxel, as First Line Therapy in Women With HER2 Positive Locally Advanced or Metastatic Breast Cancer	Everolimus 10 mg daily + paclitaxel 80mg/m^2 days 1, 8, 15 + trastuzumab 2 mg/kg days 1, 8, 15, 22 vs Placebo + paclitaxel 80 mg/m^2 days 1, 8, 15 + trastuzumab 2 mg/kg days 1, 8, 15, 22	PFS OS ORR CBR	719 Not recruiting
NCT01007942 Phase III	Novartis Pharmaceuticals	A Randomized Phase III, Double-blind, Placebo-controlled Multicenter Trial of Daily Everolimus in Combination With Trastuzumab and Vinorelbine, in Pretreated Women with HER2/Neu Over-Expressing Locally Advanced or Metastatic Breast Cancer	Everolimus + vinorelbine + trastuzumab vs placebo + vinorelbine + trastuzumab. Doses not reported.	PFS OS ORR Patient reported outcomes CBR	569 Not recruiting

Continued

NCT00567554 Phase III	German Breast Group	A Phase III Trials Program Exploring the Integration of Bevacizumab, Everolimus (RAD001), and Lapatinib into Current Neoadjuvant Chemotherapy Regimes for Primary Breast Cancer	Epirubicin + cyclophosphamide + docetaxel with or without bevacizumab vs paclitaxel with or without everolimus vs epirubicin + cyclophosphamide + docetaxel with trastuzumab or lapatinib	pCR Toxicity RR DFS OS	2600 Not recruiting
NCT00570921 Phase II	University of Kentucky	A Phase II Study of Combined Fulvestrant (Faslodex) and RAD001 (Everolimus) in Advanced/Metastatic Breast Cancer after Aromatase Inhibitor Failure	Everolimus 10 mg daily + fulvestrant 500 mg day 1, 14, 28	TTP RR CBR Toxicity	44 Recruiting
NCT00863655 Phase III	Novartis Pharmaceuticals	A Randomized Double-Blind, Placebo-Controlled Study of Everolimus in Combination with Exemestane in the Treatment of Postmenopausal Women with Estrogen Receptor Positive Locally Advanced or Metastatic Breast Cancer Who Are Refractory to Letrozole or Anastrozole	Everolimus 10 mg daily + exemestane 25 mg daily vs placebo + exemestane 25 mg daily	PFS OS ORR Toxicity QOL	724 Not recruiting
NCT00912340 Phase II	Emory University	Randomized Phase II Trial of Trastuzumab or Everolimus in Hormone-Refractory Metastatic Breast Cancer	Trastuzumab 6 mg/kg every 3 weeks (8 mg/kg loading dose) vs everolimus 10 mg daily	RR CBR PFS	80 Recruiting
NCT00930930 Phase II	Vanderbilt-Ingram Cancer Center	A Phase II Neo-Adjuvant Study of Cisplatin, Paclitaxel With or Without RAD001 in Patients with Triple-negative Locally Advanced Breast Cancer	Cisplatin 25 mg/m^2 weekly + everolimus 5 mg daily for 1 week followed by cisplatin 25 mg/m^2 + paclitaxel 80 mg/m^2 weekly + everolimus 5 mg daily for 11 weeks vs cisplatin 25 mg/m^2 weekly + placebo daily for 1 week followed by cisplatin 25 mg/m^2 + paclitaxel 80 mg/m^2 weekly + placebo daily for 11 weeks	pCR Number of breast conservation surgery Clinical response	145 Recruiting
NCT00317720 Phase I-II	M.D. Anderson Cancer Center	Phase I-II Study of Trastuzumab in Combination with RAD001 in Patients with HER-2 Overexpressing, PTEN-Deficient Metastatic Breast Cancer Progressing on Trastuzumab-Based Therapy	Trastuzumab loading dose 8 mg/kg daily; maintenance dose 6 mg/kg every 21 days + everolimus 10 mg daily	Optimal dose ORR Biomarkers of response	47 Not recruiting
NCT00934895 Phase I-II	University of Medicine and Dentistry New Jersey	Phase I/II Study of Weekly Abraxane and RAD001 in Women With Locally Advanced or Metastatic Breast Cancer. A Study of the Cancer Institute of New Jersey Oncology Group (CINJOG)	Abraxane + everolimus 5 mg daily with escalation protocol	Optimal dose ORR Toxicity	72 Recruiting
NCT01627067 Phase II	M.D. Anderson Cancer Center	Circulating FGF21 Levels and Efficacy of Exemestane, Everolimus and Metformin in Postmenopausal Women with Hormone Receptor Positive Metastatic Breast Cancer and BMI >/= 25	Exemestane 25 mg daily + everolimus 10 mg daily + metformin 500 mg daily with escalation to 1000 mg twice daily	PFS	40 Recruiting
NCT01127763 Phase II	New York University School of Medicine	Phase II Trial of RAD001 Plus Carboplatin in Patients With Triple-Negative Metastatic Breast Cancer	Carboplatin AUC 4 every three weeks + everolimus 5 mg daily	ORR Toxicity PFS	28 Not recruiting

Continued

NCT01283789 Phase II	University of Kansas	Phase II Trial of Lapatinib and RAD-001 for HER2 Positive Metastatic Breast Cancer	Everolimus 5 mg daily + lapatinib 1250 mg daily	ORR PFS CBR	45 Recruiting
NCT01088893 Phase II	Organisation for Oncology and Translational Research	A Randomized Study of mTOR Inhibition by RAD001 (Everolimus) in Invasive Breast Cancer Patients After Pre-Operative Use of Anthracycline and/or Taxane-Based Chemotherapy	Everolimus 10 mg daily for 3 weeks, 1 week after completion of neoadjuvant treatment and before surgery	Change of biomarkers in pre- and post-surgery samples	50 Recruiting
NCT01773460 Phase II	German Breast Group	A Multicenter Randomized, Double Blind, Placebo-Controlled, Phase II Study to Compare Endocrine Treatment Alone Versus Endocrine Treatment With Everolimus in Patients With HR+/HER2− Metastatic Breast Cancer and Progression After Previous Treatment with Exemestane and Everolimus	Everolimus is given beyond progression vs placebo is given beyond progression	PFS OS CBR Toxicity Biological markers	134 Recruiting
S1207 Phase III	SWOG/NSABP	A phase III randomized, placebo-controlled clinical trial evaluating the use of adjuvant endocrine therapy +/− one year of everolimus in patients with high-risk, hormone receptor (HR)-positive and HER2-negative breast cancer: SWOG/NSABP S1207	Physician's choice adjuvant endocrine therapy + everolimus 10 mg daily for one year vs physician's choice adjuvant endocrine therapy + placebo	DFS OS Safety Adherence QOL	3500 Recruiting

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