

mTOR inhibition in management of advanced breast cancer

Shona Nag

Department of Medical Oncology,
Jehangir Hospital and Medical
Centre, Pune, Maharashtra, India

Address for correspondence:

Dr. Shona Nag,
Department of Medical Oncology,
Jehangir Hospital and Medical
Centre, Pune - 411001,
Maharashtra, India.
E-mail: shona_nag@hotmail.com

ABSTRACT

The mTOR pathway is becoming increasingly important in several cancers including breast cancer. This review will focus on the role of its inhibition in the management of advanced breast cancer.

Key words: Apoptosis, everolimus, hormone

INTRODUCTION TO mTOR INHIBITORS

Mammalian target of rapamycin (mTOR) is well recognized as serine/threonine protein kinase important for cellular growth, proliferation, motility and survival. It belongs to the family of phosphatidylinositol 3-kinase-related kinases. Its pathway is stimulated by several ligands including insulin and related growth factors (IGF-1 and IGF-2). Its dysregulation is associated with several diseases including several malignancies.^[1]

Sirolimus: The first mTOR inhibitor identified was sirolimus (also known as rapamycin). It was first discovered as a product of the bacterium *Streptomyces hygroscopicus* in a soil sample from Easter Island, an island also known as Rapa Nui, hence the name.^[1] It was approved by US FDA in 1999. It was initially developed as an antifungal drug. However its unique properties made it effective as an immunosuppressant drug used to prevent rejection in organ transplantation (marketed as Rapamune). Later it was found to prevent activation of T cells and B-cells by inhibiting their response to interleukin-2 (IL-2), a fact initially exploited for the benefit of cancer patients.

Temsirolimus (Torisel): Also known as CCI-779 (cell cycle inhibitor-779), it is a derivative of sirolimus and goes after

the same target. It went through a large phase 2 trial for the treatment of multiple sclerosis (MS), at whose completion, Wyeth decided to shelve further development. This was due to serious but rare cases of interstitial lung disease, bowel perforation, and acute renal failure. On May 30, 2007, US FDA dispelled these fears by approving it for the treatment of advanced renal cell carcinoma (RCC).^[2]

Everolimus: Also called RAD001, is the new kid on the block! The rest of this paper shall focus on everolimus. (Ridaforolimus/Deforolimus is also currently being evaluated.)

EVEROLIMUS

As an oral inhibitor of mammalian target of rapamycin (mTOR), it is also a derivative of and functions like Rapamycin (sirolimus). It does this by allosterically binding with high affinity to the FK506 binding protein-12 (FKBP-12). This drug complex in turn inhibits the activation of mTOR. Like other mTOR inhibitors, action of everolimus is solely on the mTORC1 protein (leaving the mTORC2 protein unaffected).^[3]

This inhibition has cascading effect on the downstream effectors, resulting in arrest of cell between G1 and S phase of the cell cycle. This ultimately leads to inhibition of hypoxia-inducible factor, cell proliferation and angiogenesis as well as reduction in vascular endothelial growth factor and glucose uptake - leading to cell growth arrest and apoptosis. In breast cancer cells, this effect is synergistically enhanced when combined with aromatase inhibition.^[4]

Everolimus was first approved by US FDA in 2009.^[5] It is

Access this article online

Quick Response Code:



Website:
www.ijmpo.org

DOI:
10.4103/0971-5851.99737

available as tablets of various strengths (2.5 mg, 5 mg and 10 mg). It is recommended to be taken once daily at the same time, consistently with or without food. Severe or intolerable adverse reactions may require temporary dose reduction (to 5 mg) and/or interruption of treatment. For moderate hepatic impairment (Child-Pugh class B), reduce the dose to 5 mg daily. The use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) should be avoided. When co-administered with moderate CYP3A4 and/or P-gP inhibitors (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem), the dose of everolimus needs to be reduced to 2.5 mg daily. If this moderate inhibitor is discontinued, a washout period of approximately 2 to 3 days should be allowed before the everolimus dose is increased. If it is unavoidable to use concomitantly with strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital), dose of everolimus needs to be increased from 10 mg daily up to 20 mg daily (based on pharmacokinetic data), using 5 mg increments. Grapefruit and grapefruit juice (foods known to inhibit cytochrome P450 and P-gP activity) may increase everolimus exposures and should be avoided. Peak everolimus concentrations are reached 1 to 2 hours after administration of oral doses. High fat meals reduced systemic absorption and circulating blood levels. Major route of excretion from the body is through the feces (80%). An additional small amount (5%) is eliminated in the urine (5%). Elimination half life is 30 hours.

Everolimus is already approved in more than 80 countries for four indications (the oncology ones being advanced renal cell carcinoma, giant cell astrocytoma and neuroendocrine tumors of pancreas). Breast cancer will be the fifth indication.^[6]

It is marketed under various trade names: Zortress (USA) and Certican (Europe and other countries) in transplantation medicine; Afinitor and Votubia in oncology.

EVEROLIMUS CLINICAL TRIALS AND BREAST CANCER

BOLERO-2 was an international, double-blind, phase 3 study in which patients were randomised in a 2:1 ratio between oral everolimus and matching placebo (at a dose of 10 mg daily).^[7] All patients received exemestane in the dose of 25 mg daily. Randomization was stratified for visceral metastasis and sensitivity to endocrine therapy (adjuvant treatment for at least 24 months with endocrine therapy before recurrence or a response/ stabilization for at least

24 weeks of endocrine therapy for advanced disease). The primary end point of the study was progression-free survival (PFS).

This trial was conducted at 189 global sites (24 countries) and enrolled 724 women having a median age of 62 years. Their baseline characteristics were well balanced between the two study groups. The key inclusion criteria are shown in Table 1.

In hormone receptor positive breast cancer cells, endocrine resistance develops as a result of aberrant signaling through the phosphatidylinositol 3-kinase (PI3K)-Akt-mTOR pathway.^[8-10] One of S6 kinase 1 is the substrates of the mTOR complex 1 (mTORC1) that phosphorylates the activation function domain 1 of the ER and leads to ligand-independent receptor activation. Thus, resistance to endocrine therapy is associated with activation of the mTOR intracellular signaling pathway.

As of February 11, 2011, a total of 296 patients were still receiving study treatment: 227 (47%) in the combination-therapy group and 69 (29%) in the exemestane-alone group. The median duration of exposure to everolimus was 14.6 weeks in study arm as compared with 12.0 weeks of exposure to placebo. Disease progression led to discontinuation in 37% patients among the combination-therapy group as compared to 66% in the exemestane-alone group [Table 2].

The primary end point was the median progression-free survival. It was 6.9 months for everolimus plus exemestane versus 2.8 months for placebo plus exemestane (hazard ratio for progression or death, 0.43; 95% confidence interval (CI), 0.35 to 0.54; $P < 0.001$) as per investigator's assessment. On central assessment, these figures were 10.6

Table 1: Key inclusion criteria of BOLERO-2 study

Postmenopausal women
ER-positive
Human epidermal growth factor receptor type 2 (HER2)-nonamplified
Advanced breast cancer
Disease was refractory to previous letrozole or anastrozole
a. recurrence during or within 12 months after the end of adjuvant treatment or
b. progression during or within 1 month after the end of treatment
Letrozole or anastrozole did not have to be the most recent treatment before randomization
recurrence or progression during the most recent systemic therapy had to be documented
Other previous anticancer endocrine treatments and a single prior chemotherapy regimen for advanced disease were permitted
Lack of brain metastasis
No previous exposure to mTOR inhibitors or exemestane

Table 2: Results of BOLERO-2 study (International, double-blind, phase 3 study conducted at 189 global sites (24 countries) involving 724 postmenopausal HR +ve Her2 -ve advanced breast cancer women)

	Everosolimus arm	Control arm
Patients still on study Rx (%)	227 (47)	69 (29)
Median duration of study Rx	14.6 weeks	12 weeks
Discontinuation due to PD, %	37	66
Median PFS (Investigator)	6.9 months	2.8 months
Median PFS (Central)	10.6 months	4.1 months
Updated median PFS (Investigator)	7.4 months	3.2 months
Updated median PFS (Central)	11 months	4.1 months
RR	12.5	1.3%
Clinical benefit, %	50.5	25.5
Deaths (Updated), %	17.2	22.7

months and 4.1 months respectively (hazard ratio, 0.36; 95% CI, 0.27 to 0.47; $P < 0.001$). Interestingly the central assessment actually led to increase in the progression free times in both the arms. At the San Antonio Breast Cancer Symposium (SABCS) last year and the Early Breast Cancer Congress (EBCC) meeting earlier this year, the updated findings showed a PFS of 7.4 months for the everolimus arm as compared to 3.2 months for the control arm.^[11,12] Response rates and clinical benefit rates (patients with complete response, partial response, or stable disease for greater than six months) were higher in the combination arms (12.0% vs. 1.3% and 50.5% vs. 25.5%; $P < 0.0001$), respectively. The benefit was seen regardless of the presence of visceral disease, prior use of chemotherapy or number of prior therapies. In addition, patients with only bone metastases benefited from the combination. These results represent an additional five months of follow-up (median duration of follow-up of 17.5 months)

These results are similar to the benefit seen with chemotherapy (without their toxicity). For instance, the median PFS with capecitabine, taxanes or anthracyclines also ranges between 6.2 months and 8.2 months.^[13]

Corresponding figures for overall response rates (ORR) were 9.5% and 0.4% respectively ($P < 0.001$). It is still too early to discuss overall survival (OS) as longer follow up and greater number of events are awaited. As per the cut off date for these results, 83 deaths have occurred of which 10.7% of patients were in the combination-therapy group and 13.0% in the exemestane-placebo group.

Important grade 3 or 4 adverse events were stomatitis (8% in the everolimus-plus-exemestane group vs. 1% in the placebo-plus-exemestane group), anemia (6% vs. <1%),

dyspnea (4% vs. 1%), hyperglycemia (4% vs. <1%), fatigue (4% vs. 1%), and pneumonitis (3% vs. 0%).

At the time of updated analysis, 137 patients died, constituting 17.2% of patients in the everolimus plus exemestane arm and 22.7% of those in the exemestane-only arm.

Bachelot T *et al.* reported results of a trial of everolimus plus tamoxifen for ER-positive, HER2-negative, metastatic disease at last year's SABCS.^[14]

In 2009, Dr. Baselga and colleagues reported results of the study in newly diagnosed breast cancer patients given neoadjuvant everolimus combined with letrozole. They showed that there was improvement in the clinical response rate and reduction in the tumor-cell proliferation as compared to letrozole alone.^[15]

In a randomized phase 2 study with similar patient group (postmenopausal women with ER-positive advanced breast cancer) but previously treated with an aromatase inhibitor, everolimus - tamoxifen combination led to improved PFS as compared to tamoxifen alone (8.6 months vs. 4.5 months, $P = 0.002$). In addition the study arm led to significantly better OS as well (median not reached vs. 24.4 months, $P = 0.01$).^[16]

Another interesting study presented at SABCS Dec 2011, combined everolimus with cisplatin and paclitaxel in heavily pretreated Her2 negative patients with metastatic breast cancer.^[17] Members of the p53 gene family are involved in development, differentiation, and response to cellular stress. It is known that p63 and p73 work in opposite directions. So increasing p73 activity and/or decreasing p63 expression will increase apoptosis and reduce tumorigenesis. Since cisplatin and mTOR increase p73 activity whereas paclitaxel decreases p63 expression, this seems to be an ideal three drug combination to be evaluated. Besides p53 and p73 promote apoptosis in response to DNA damage and p53 mutations are seen in about a third of breast cancers (usually in aggressive, hormone receptor negative patients).

This single arm, open-label, multicenter phase II trial used cisplatin 25 mg/m² plus paclitaxel 80 mg/m² on Days 1, 8, and 15 every 28 days along with everolimus 5 mg/day orally. The treatment was continued until disease progression or unacceptable toxicity. The primary aim was to measure TTP. More than half (62.5%) of patients were triple negative and in 54% of cases metastasis was detected at diagnosis or within 24 months of previous treatment. It resulted in an ORR 23.4 % and median TTP of 5 months. The most common grade 3 and 4 toxicities were anemia (16%) and

neutropenia (28%), febrile neutropenia occurring in only 1%; even among heavily pretreated patients, only 13% discontinued treatment due to toxicity.

Table 3 summarises the current trials using Everolimus in Breast Cancer. Besides breast cancer, phase III trials have been done/ are under way in gastric cancer, hepatocellular carcinoma and lymphoma.^[18-21]

SIDE EFFECTS

Side effects include hematological, metabolic, dermatological, gastrointestinal, respiratory, hypersensitivity, musculoskeletal, cardiovascular, ocular, renal and related to the nervous system. However most of them are minor and/or infrequent. Grade 3 or 4 side effects seen in more than 4 % of the patients included stomatitis, anemia, fatigue, hyperglycemia and elevated liver enzymes. They

can be an impediment in for prolonged use of this drug in affected patients.^[7]

FUTURE OF EVEROLIMUS IN BREAST CANCER

On June 22, 2012 it was announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion for everolimus tablets, in combination with exemestane, for the treatment of hormone receptor-positive (HR+), HER2/neu-negative (HER2-) advanced breast cancer, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.^[22,23] The European Commission generally follows the recommendations of the CHMP and usually delivers its final decision within three months of the CHMP recommendation. The decision will be

Table 3: Current breast cancer trials with everolimus

Phase (Protocol ID)	Study title
Phase: Phase II (Protocol IDs: HP-00040802, GCC 0901, NCT01499160)	Study of how well letrozole works in combination with lapatinib followed by an addition of everolimus in postmenopausal women with advanced endocrine resistant breast cancer
Phase II (Protocol IDs: WCL1711-09, NCT01272141)	A study of lapatinib in combination with everolimus in patients with advanced, triple negative breast cancer
Phase II (Protocol IDs: AIO-MAM-0110, 2011-001024-38, NCT01520103)	Study to compare vinorelbine in combination with the mTOR inhibitor everolimus vs. Vinorelbin monotherapy for second-line treatment in advanced breast cancer
Phase II (Protocol IDs: OOTR-No06, NCT01088893)	Everolimus in breast cancer patients after pre-operative chemotherapy
Phase II (Protocol IDs: LCCC 1025, 11-0242, NCT01305941)	A study of everolimus, trastuzumab and vinorelbine in HER2-positive breast cancer brain metastases
Phase II (Protocol IDs: WCL1524-08, NCT00912340)	Randomized phase II trial of trastuzumab or EVEROLIMUS in hormone-refractory metastatic breast cancer
Phase II, Phase I (Protocol IDs: CRAD001JDE15T, NCT00930475)	Everolimus (RAD001) and carboplatin in pretreated metastatic breast cancer
Phase II (Protocol IDs: 12418, NCT01283789)	Lapatinib and RAD-001 for HER2 positive metastatic breast cancer
Phase III (Protocol IDs: CRAD001W2301, 2008-008697-31, NCT01007942)	Daily everolimus in combination with trastuzumab and vinorelbine in HER2/Neu positive women with locally advanced or metastatic breast cancer
Phase II (Protocol IDs: VICC BRE 0904, P30CA068485, VU-VICC-BRE-0904, IRB# 090291, NCT00930930)	Cisplatin and paclitaxel with or without everolimus in treating patients with stage II or stage III breast cancer
Phase III (Protocol IDs: CRAD001J2301, 2008-006556-21, NCT00876395)	Everolimus in combination with trastuzumab and paclitaxel in the treatment of HER2 positive locally advanced or metastatic breast cancer
Phase II (Protocol IDs: 2011-1239, NCT01627067)	FJE_exemestane-RAD001-metformin
Phase II, Phase I (Protocol IDs: 040803, P30CA072720, CDR0000648116, 0220090058, CRAD001C2448, CINJ-040803, NOVARTIS-CINJ-040803, NCT00934895)	Phase I/II study of weekly abraxane and RAD001 in women with locally adv. Or metastatic breast Ca
Phase II (Protocol IDs: NYU 09-0060, NCT01127763)	RAD001 plus carboplatin in breast cancer patients
Phase II (Protocol IDs: 12186, NCT01163929)	A study to look at the combination of chemotherapy, trastuzumab and RAD001 in HER2 positive breast cancer
Phase I (Protocol IDs: CRAD001X2109, 2011-001425-24, NCT01482156)	Dose finding study of RAD001 (Everolimus, Afinitor®) in combination with BEZ235 in patients with advanced solid tumors
Phase IV (Protocol IDs: CRAD001JIL05, NCT01231659)	Safety and efficacy of RAD001 (Everolimus) in combination with letrozole in the treatment of postmenopausal women with locally advanced or metastatic breast cancer
Phase II (Protocol IDs: 07-BRE-43-NP, NCT00570921)	Study of combined fulvestrant and RAD001 in advanced/metastatic breast cancer after aromatase inhibitor failure
Phase II (Protocol IDs: CDR0000595159, FRE-FNCLCC-GEP-04/0606-RAD-HER, EUDRACT-2007-004098-24, EU-20851, FRE-FNCLCC-GEP 04/0606 - RAD-HER, RAD-HER, NCT00674414)	Trastuzumab with or without everolimus in treating women with breast cancer that can be removed by surgery

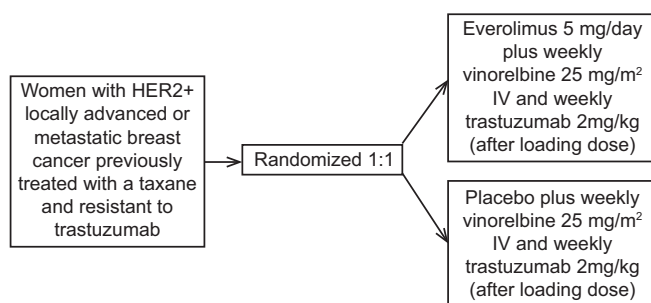
applicable to all 27 European Union member states plus Iceland and Norway. Everolimus is currently being considered in this patient population for approval by the US Food and Drug Administration, the Swiss Agency for Therapeutic Products (Swissmedic) and by health authorities worldwide.

Everolimus is also being studied in HER2-positive breast cancer in two Phase III trials [Figure 1].^[24]

Agents inhibiting the phosphoinositide 3-kinase-Akt-mammalian target of rapamycin (PAM) pathway have been associated with metabolic toxicities of hyperlipidemia and hyperglycemia. The PAM Task Force of the National Cancer Institute Investigational Drug Steering Committee convened an interdisciplinary expert panel to review the pathophysiology of such hyperlipidemia and hyperglycemia.^[25] Their conclusion is that Dose modifications or discontinuation of PAM pathway inhibitors should only be considered if such metabolic toxicities are severe and persists even after their treatment has been administered for sufficiently long time.

It is well established that hormonal therapy is the key to successful treatment of advanced breast cancer. Yet a significant number of patients with metastatic disease do not respond to initial treatment and the vast majority, in fact, will ultimately develop resistance. Our approach to counter this was the sequential use of as all possible hormone therapies available to us with the aim of keeping longest possible control over the malignancy.

Everolimus has the potential to disrupt this thinking, be a game changer. It represents a major innovation in HR+/HER2-advanced breast cancer, something we have been waiting for since aromatase inhibitors were introduced more than 15 years ago. This approach promises to address an important unmet need for hundreds of thousands of women with hormone receptor expressing advanced disease.^[26]



Phase III, randomized, double-blind study

Figure 1: BOLERO-3 study design

REFERENCES

- Vézina C, Kudelski A, Sehgal SN. Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. *J Antibiot* (Tokyo) 1975;28:721-6.
- Available from: <http://www.cancer.gov/cancertopics/druginfo/fda-temsirolimus>. [Last Accessed on 2011 Apr 7]
- Yamnik RL, Holz MK. mTOR/S6K1 and MAPK/RSK signaling pathways coordinately regulate estrogen receptor alpha serine 167 phosphorylation. *FEBS Lett* 2010;584:124-8.
- Everolimus in combination with trastuzumab and paclitaxel in the treatment of her2 positive locally advanced or metastatic breast cancer (BOLERO-1). Available from: <http://www.clinicaltrials.gov/ct2/show/NCT00876395?term=bolero-1&rank=1>. [Last Accessed on 2011 Nov]
- Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, *et al*. Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. *Cancer* 2010;116:4256-65.
- Yuan R, Kay A, Berg WJ, Lebwohl D. Targeting tumorigenesis: Development and use of mTOR inhibitors in cancer therapy. *J Hematol Oncol* 2009;2:45.
- Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahmoud T, *et al*. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012;366:520-9.
- Burstein HJ. Novel agents and future directions for refractory breast cancer. *Semin Oncol* 2011;38 Suppl 2:S17-24.
- Johnston SR. Clinical efforts to combine endocrine agents with targeted therapies against epidermal growth factor receptor/human epidermal growth factor receptor 2 and mammalian target of rapamycin in breast cancer. *Clin Cancer Res* 2006;12:1061s-1068s.
- Schiff R, Massarweh SA, Shou J, Bharwani L, Mohsin SK, Osborne CK. Cross-talk between estrogen receptor and growth factor pathways as a molecular target for overcoming endocrine resistance. *Clin Cancer Res* 2004;10:331S-6S.
- Hortobagyi GN. Everolimus for postmenopausal women with advanced breast cancer: Updated results of the BOLERO-2 phase III trial. 2011 San Antonio Breast Cancer Symposium (SABCS) Updated late breaking abstract No. S3-7. December 7, 2011).
- Gnant M, Beermann B. 8th European Breast Cancer Conference (EBCC-8), Vienna, March 21-24, 2012. *Breast Care* (Basel) 2012;7:170-6.
- Robert NJ, Diéras V, Glaspy J, Brufsky AM, Bondarenko I, Lipatov ON, *et al*. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J Clin Oncol* 2011;29:1252-60.
- Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, Ferrero JM, Freyer G *et al*. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: A GINECO study. *J Clin Oncol* 2012;30:2718-24.
- Baselga J, Semiglazov V, van Dam P, Manikhas A, Bellet M, Mayordomo J, *et al*. Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. *J Clin Oncol* 2009;27:2630-7.
- Bachelot T, Bourgier C, Cropet C, *et al*. TAMRAD: a GINECO randomized phase II trial of everolimus in combination with tamoxifen versus tamoxifen alone in patients (pts) with hormone-receptor positive, HER2 negative metastatic breast cancer (MBC) with prior exposure to aromatase inhibitors

- (AI). Presented at the 33rd Annual San Antonio Breast Cancer Symposium. San Antonio, Texas: 2010. Dec 8-12.
17. Mayer IA, Means-Powell J, Abramson VG, *et al.* Phase II trial of RAD001 (everolimus), an mTOR inhibitor with weekly cisplatin and paclitaxel in patients with HER2-negative metastatic breast cancer. Program and abstracts of the 34th Annual San Antonio Breast Cancer Symposium. San Antonio, Texas: 2011. December 6-10. Abstract PD09-06.).
 18. Fasolo A, Sessa C. Targeting mTOR pathways in human malignancies. *Curr Pharm Des* 2012;18:2766-77.
 19. Al-Batran SE, Ducreux M, Ohtsu A. mTOR as a therapeutic target in patients with gastric cancer. *Int J Cancer* 2012;130:491-6.
 20. Coiffier B, Ribrag V. Exploring mammalian target of rapamycin (mTOR) inhibition for treatment of mantle cell lymphoma and other hematologic malignancies. *Leuk Lymphoma* 2009;50:1916-30.
 21. Frenette C, Gish R. Targeted systemic therapies for hepatocellular carcinoma: clinical perspectives, challenges and implications. *World J Gastroenterol* 2012;18:498-506.
 22. Available from: <http://www.genengnews.com/gen-news-highlights/novartis-afinitor-cleared-by-fda-for-treating-sega-tumors-in-tuberous-sclerosis/81244159/>. [Last Accessed on 2012 Mar 16].
 23. Available from: <http://www.genengnews.com/gen-news-highlights/positive-trial-data-leads-novartis-to-plan-breast-cancer-filing-for-afinitor-by-year-end/81245384/>. [Last Accessed on 2012 Mar 16].
 24. Daily everolimus in combination with trastuzumab and vinorelbine in her2/neu positive women with locally advanced or metastatic breast cancer (BOLERO-3). Available from: <http://clinicaltrials.gov/ct2/show/NCT01007942?term=BOLERO-3&rank=1>. [Last Accessed on 2011 Nov].
 25. Busaidy NL, Farooki A, Dowlati A, Perentesis JP, Dancey JE, Doyle LA, *et al.* Management of Metabolic Effects Associated With Anticancer Agents Targeting the PI3K-Akt-mTOR Pathway. *J Clin Oncol* 2012.
 26. World Cancer Report. International agency for research on cancer. Available from: <http://globocan.iarc.fr/factsheets/populations/factsheet.asp?uno=900>. [Last Accessed on 2011 Dec].

How to cite this article: Nag S. mTOR inhibition in management of advanced breast cancer. *Indian J Med Paediatr Oncol* 2012; 33:89-94.

Source of Support: Nil, **Conflict of Interest:** None declared.