Review Article

Efficacy of Everolimus in Treating Breast Cancer

Dr. Hari Chandana Punukula*
PharmD, Bharat institute of Technology, Hyderabad, Telangana, India.
***Corresponding author's E-mail:** harichandana5997@gmail.com

Received: 18-08-2020; **Revised:** 15-10-2020; **Accepted:** 24-10-2020; **Published on:** 15-11-2020.

ABSTRACT

The mammalian purpose of rapamycin (mTOR) has been found to gather insights into their essential role in pathogenesis of breast cancer. hMany clinical trials have shown that the mTOR everolimus inhibitor can enhance patient results for several sub-types of breast cancer, including harmone receptor-positive, human-epidermal growth factor receptor-negative metastatic disease that has developed, followed by endocrine therapy. This analysis summarises the results of clinical studies that support the efficacy of everolimus in metastatic breast cancer, and discusses several new research directions for everolimus.

Keywords: Hormone receptor–positive, mTOR, everolimus, endocrine resistance.

QUICK RESPONSE CODE →

DOI:
10.47583/ijpsrr.2020.v65i01.007

DOI link: http://dx.doi.org/10.47583/ijpsrr.2020.v65i01.007

INTRODUCTION

After the discovery of the role of estrogens in this disease, our understanding of the molecular pathogenesis of breast cancer has changed exponentially. More understanding of the many subtypes of breast cancer in recent years has led to the discovery of several new therapeutic targets for each molecular pathogenesis.

In both early and advanced-stage cases, nearly 75 percent of patients with breast cancer have HR-positive (hormone receptor) tumours. This sub-type of breast cancer initially has a high overall rate of response to hormonal therapies such as selective modulating oestrogen receptor (ER), selective ER down-regulators (e.g. fulvestrant) and aromatase inhibitors (e.g. anastrozole, letrozole and exemestane) inhibitors. However, endocrine therapy resistance grows finally. Furthermore, some tumours have de novo resistance to endocrine treatment. Both de novo and acquired resistance result in progression of the tumour; therefore, to control HR-positive breast cancer, overcoming such a resistance is necessary[1, 2].

EVEROLIMUS

The everolimus mTOR inhibitor, a sirolimus (also referred by rapamycin), is a protein in the immunophiline family that is very similar to its intracellular receptor FKBP12. The everolimus-FKBP12 complex prevents mTOR from signalling downstream in cell cycle development, cell growth and proliferation. A Phase II study with a single-agent daily or weekly everolimus therapy showed moderate clinical results, which range from 0 to12 percent, in patients with metastatic breast cancer[3]. However, in patients with metastatic breast cancer resistant to hormone therapies, everolimus has been tested in association with exemestane and patient findings have been confirmed, with approvals from the United States Food and Drug Administration (FDA) [4]. In 2012, in the framework of their recommendations for treating HR positive metastatical breast cancer, the National Comprehensive Cancer Network Guidelines added the everolimus /exemestane combination[5]. The promising effects of everolimus plus exemestane therapy have shown that blocking a breast cancer escape route clinically improves hormone sensitivity[6].

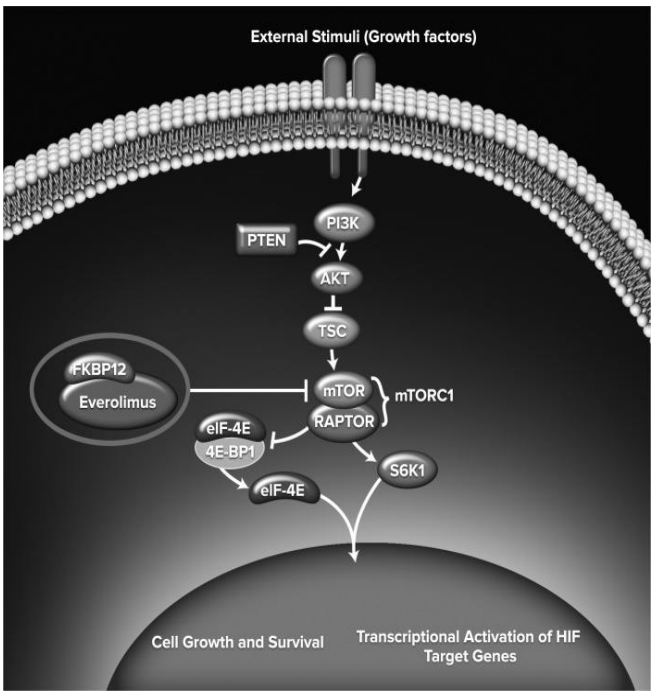

Figure 1: Mechanism of Action of Everolimus

EVEROLIMUS IN HARMONE RECEPTOR POSITIVE DISEASE

BOLERO-2 (Breast Cancer Trial of Oral Everolimus-2) study

The FDA has approved the everolimus plus exestane combination to treat HR-positive, human-epidermal growth factor receptor2 (HER2) after failure of treatment with letrozole or anastrozole based on the results of the Phase III BOLERO 2 randomised study[7]. The findings of the BOLERO-2 analysis demonstrated the substantial improvement in progression free survival (PFS) of everolimus plus exemestane over around 4 months. Median PFS for the everolimus plus exemestane group based on local assessment was 6.9 months versus 2.8 months for the exemestane plus placebo group (hazard ratio, 0.43; 95% confidence interval [CI], 0.35–0.54; *P* < 0.0001)[8, 9, 10]. Further review with the BOLERO-2, 18-month follow-up data, resulted in clear median PFS findings (local assessment 7.8 versus 3.2 months; hazard ratio 0.45; 95 percent CI, 0.35 versus 0.54; P < 0.0001). The BOLERO-2 study's revised findings, while showing no statistical substantial difference in overall survival (OS), represented the most long-reported OS in post-nonsteroidal aromatase, with approximately 31 months of OS seen in Everolimus plus exemestane placebo.The BOLERO-2 study's revised findings, while showing no statistical substantial difference in overall survival (OS), represented the most long-reported OS in post-nonsteroidal aromatase, with approximately 31 months of OS seen in Everolimus plus exemestane placebo. tEverolimust + exemestane is usually well tolerated, the most common adverse effects were stomatitis (59%), rash (39%), tiredness (37%) and diarrhoea (34%), nausea (31%) and reduced apetite (35%). The most common adverse effects were stomatitis (8%), anaemia (7%), dyspnea (5%), hyperglycemia (5%), and fatigue (3%). Non-infectious pneumonitis (which was a significant deterioration of respiratory function by ground glass – presence of ears or patches in the compute scans of tomography) were the less common yet life threatening adverse events. This toxicity was apparently mediated immunologically and its medication interruption and corticosteroids were often needed in the clinical management. BOLERO-2 results also revealed that more patients stopped their treatment with everolimus plus the exemestane arm (26% versus the 50%) due to adverse effects than with placebo plus the exemestane arm[11].

TAMRAD trial

BOLERO-2 was a randomised PhaseII trial in HR-positive / HER2-negative metastatic breast cancer patients with previous exposures to aromatase inhibitors which investigated the everolimus + tamoxifene association compared with tamoxifen alone. The everolimus plus tamoxifen (n= 54) was allocated to patients randomly or tamoxifen alone (n=57). At a median follow-up rate of 22 months, the clinical benefits rate was 61.1 percent in the everolimous plus tamoxifen arm compared with 42.1 percent in the tamoxifen-alone arm (p = 0.045). The median time of development was 8.6 months compared with 4.5 months (P= 0.0026)[12, 13]. For patients who initially reacted to inhibitors of aromatases and then became resistant this strategy was promising, but those with primary hormone tolerance did not benefit from everolimus adding to tamoxifen.

BRE-43 study

Moreover, in patients with ER-positive metastatic breast cancer whose condition worsened or relapsed on an inhibctor of aromatase within 6 months of entry, a phase II singlearm experiment evaluated everolimus together with fulvestrant. The median progression period was 7.4 months (95 % CI, 1, 9% – 12, 1%) and median OS was 24 months (95 % CI, 18, 3%–28, 7), among 31 patients available for study. In the 8-week evaluation of radiological diseases, a third of the patients demonstrated de novo resistance to medication[14, 15].

EVEROLIMUS IN OTHER BREAST CANCER SUBTYPES

HER2-positive tumors

Up to 30% of breast cancers express the HER2 receptor and trigger signal pathways to be activated that promote cell proliferation and survival. In patients with HER2-positive breast cancer, HER2-targeted treatment has greatly improved outcomes. Like HR-positive breast cancer therapies, de novo as well as anti HER2 therapy resistance can be acquired. Trastuzumab resistance is due to aberrant PI3 K pathway activation of the monoclonal antibody used as a treatment for early stage HER2-pacific breast cancer[16]. This resistance can be linked to phosphatase and tensin homolog (PTEN) loss and dysregulation[17]. A large RNA interference test with 8,000 genes has only found PTEN suppression to be a mediator in HER2-overexpressing breast cancer cell trastuzumab resistance. A study and a combination of PTEN expression levels and therapeutic reactions in breast cancer patients undergoing post-trastuzumab therapy in tumour samples showed that PTEN patients had substantially lower overall reactions than the PTEN-positive tumors[18]. Activation of the pathway for PI3 K by PIK3CA mutations in patients with trastuzumab treated breast cancer was associated with shortened PFS. Increased sensitivity to PI3 K inhibitors was also demonstrated by trastuzumab resistant cells. The combination of rapamycin and trastuzumab had a synergistic effect on tumour regression in a preclinical mouse model with HER2-overexpressing breast cancer. In HER2-overexpressing models, everolimus regained the sensitivity of trastuzumab when paired with chemotherapy. Clinical studies have also centred on the use of everolimus to resolve resistance to treatments targeted at HER2-positive subtypes of breast cancer[19, 20].

Triple-negative tumors

Triple negative breast cancer is usually at an advanced stage during the diagnosis and is characterised by a lack of HER2 and HR expression. The effectiveness of the combination therapy has been demonstrated by a phase II

analysis of everolimus and carboplatin in patients with triple negative metastatic breast cancer, with a clinical benefit rate of 36% and a median PFS of 3 months. Decreasing the carboplatin dose decreased haematological toxicity while retaining clinical responses in these patients. The reaction of adding everolimus to normal neo-adjuvant chemotherapy was tested in a newly completed phase II test in patients with triple-negative breast cancer. The combination of 5-fluro-uracil, epirubicin and cyclophosphamide was given to patients every 3 weeks during four cycles for 12 weeks. There was no major difference in the response rate of 12-week groups (47.8% versus 29.6%; P = 0.075) and pathological total reaction (30.4% versus 25.9%; P = 0.76)[21].

BOLERO-4 study

In the first-line postmenopausal women with HR-positive metastatic HER2-negative breast cancer, BOLERO-4 is an open-label phase II, multiple centre analysis with everolimus plus letrozole. BOLERO-4 will also examine whether the everolimus+ letrozole combination is an appropriate, first-line treatment for metastatic breast cancer and whether its success will continue with the everolimus plus exemestane combination as soon as the disease progresses. BOLERO-4 will also determine whether an alcohol-free mouth steroid rinse will lead to improving the seriousness of oral stomatitis. The study's stomatitis portion will be done in the US only if an oral solution of dexamethasone free of alcohol 0.5 mg/5 mL is available[22, 23].

Everolimus plus fulvestrant

After development on aromatase inhibitor therapy, everolimus in combination with fulvestrant is examined in another ongoing phase II study in postmenopausal women with HR-positive metastatic HER2 cancer. Patients will be assigned 1:1 randomly for Everolimus or placebo and stratified to the Eastern Cooperative Oncology success community (0 vs. 1), observable disease against non-measurable disease, and pretreatment vs. previous chemical therapy for metastatic disease. Every 12 weeks, patients are tested for a total of 12 cycles for disease response. Patients without advanced disease signs remain unblinded and continue to be treated until worsening or undesirable toxicities arise following completion of 12-cycles[24].

Detect IV trial

In the DETECT IV review, we will further improve our understanding of the effects and mechanisms of everolimus in the treatment of metastatic cancer of HR-positive HER2. The prevalence and the number of circulating tumour cells (CTCs) during treatment at different time periods has been suggested as an important method to measure the effectiveness of therapy in metastatic breast cancer. For HR-positive, HER2 negative metastatic breast cancer patients, and exclusively HER2-negative CTCs, DETECT IV is a prospective, multicenter, open-label, one-arm-phase-II study. This research aims first and foremost to predict, in conjunction with endocrine therapy as PFS, the clinical effectiveness of everolimus. A further analysis of CTC dynamics and characteristics provides a better knowledge of the predictive and prognostic value of CTCs in this context[25].

SWOG S1207

Owing to the promising findings of everolimus for advanced breast cancer diagnosis, it will be a natural next step to research its possible effect on the treatment of HR-positive, HER2-negative breast cancer using the medication to treat earlier stage disease. SWOG S1207 is a randomised Phase III study in several centres which investigates the impact of hormone therapy on patients with early stage breast cancer with or without everolimus. The aims of the study are to compare whether adding everolimus 1-year (10 mg / day) to standard endocrine-adjuvant therapy enhance the invasive disease-free survival of HR-positive, HER2-negative non-metastatic breast cancer patients. Additionally, SWOG S1207 is comparing the probability of OS, remote recurrence-free survival, protection, and tolerability in this patient population by adding 1 year of everolimus to a standard adjuvant endocrine therapy[26].

Targeting subtypes

Also explored the combination of everolimus with other standard chemotherapies used to treat other subtypes of breast cancer. One randsomised, double-blind, placebo-controlled trial is an impact evaluation for women with HER2-negative metastatic breast cancer of the effect of adding everolimus to the combination of weekly paclitaxel + bevacizumab. A patient with everolimus or placebo is assigned randomly to 1:1 paclitaxel plus bevacizumab. Every eight weeks before tumour development or irreversible toxicity occurs, patients are tested for response to treatment. Another research examins the combination of cisplatin, paclitaxel and everolimus as a neoadduvant for locally advanced threefold negative breast cancer. The primary aim of this study was to use the primary tumour as a de novo marker for exposure and responsiveness to combination therapy in pathologically complete surgical responsiveness[27]. An additional research explores the combination of vinorelbine / everolimus versus vinorelbine alone as a second-line therapy of HER2-negative, locally advanced or metastatic breast cancer where the primary endpoint is PFS.

CONCLUSION

The quest for the best combination of therapies to treat HR-positive breast cancer patients and the regulation of endocrine resistance remains a challenge for both clinicians and researchers. ER biology is interconnected naturally to many cell signalling pathways with established cross-talk feedback loops and regulatory feedback loops. The route of PI3K / mTOR / AKT is a significant doorway to resistant types of HR-positive HER2-negative breast cancer. The clinical studies outlined in this paper show that mTOR inhibition, such as everolimus, can target resistant

breast cancer types and increases endocrine sensitivity. Continuous trials with everolimus in earlier stages of the disease in adjuvant and neo-adjuvant conditions will theoretically help even more patients (where there is greater likelihood of cure).

Further pre-clinical research with human tumour samples and pharmacodynamic tissue-based experiments would need to be conducted to better understand the role of mTOR blockage and the associated modifications in other relevant routes. It is extremely important that we keep on enrolling patients in clinical trials to enhance our understanding and approaches to endocrine-resistant cancer.

REFERENCES

1. Germano S, O'Driscoll L. Breast cancer: understanding sensitivity and resistance to chemotherapy and targeted therapies to aid in personalised medicine. Curr Cancer Drug Targets. 9, 2009, 398–418.

2. Pritchard KI. Endocrine therapy: is the first generation of targeted drugs the last J Intern Med. 274, 2013, 144–152.

3. Zardavas D, Fumagalli D, Loi S. Phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin pathway inhibition: a breakthrough in the management of luminal (ER+/HER2−) breast cancers Curr Opin Oncol. 24, 2012, 623–634.

4. Wander SA, Hennessy BT, Slingerland JM. Next-generation mTOR inhibitors in clinical oncology: how pathway complexity informs therapeutic strategy. J Clin Invest. 121, 2011, 1231–1241.

5. Mayer I. Role of mTOR inhibition in preventing resistance and restoring sensitivity to hormone-targeted and HER2-targeted therapies in breast cancer. Clin Adv Hematol Oncol. 11, 2013, 217–224.

6. Lebwohl D, Thomas G, Lane HA. Research and innovation in the development of everolimus for oncology. Expert Opin Drug Discov. 6, 2011, 323–338.

7. Anandappa G, Hollingdale A, Eisen T. Everolimus—a new approach in the treatment of renal cell carcinoma. Cancer Manag Res. 2, 2010, 61–70.

8. Ellard SL, Clemons M, Gelmon KA. Randomized phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer: NCIC Clinical Trials Group IND.163. J Clin Oncol. 27, 2009, 4536–4541.

9. Baselga J, Campone M, Piccart M. Everolimus in postmenopausal hormone receptor-positive advanced breast cancer. N Engl J Med. 366, 2012, 520–529.

10. Novartis Pharmaceuticals Corporation. Afinitor (everolimus) tablets for oral administration East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2015.

11. National Comprehensive Cancer Network Inc. NCCN Clinical Practice Guidelines in Oncology, Breast Cancer Version 2. Fort Washington: NCCN, 2015.

12. Yardley DA, Noguchi S, Pritchard KI. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther. 30, 2013, 870–884.

13. Piccart M, Hortobagyi GN, Campone M. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. Ann Oncol. 25, 2014, 2357–2362.

14. Pritchard KI, Burris HA, III, Ito Y. Safety and efficacy of everolimus with exemestane vs. exemestane alone in elderly patients with HER2-negative, hormone receptor-positive breast cancer in BOLERO-2. Clin Breast Cancer. 13, 2013, 421–432.

15. Noguchi S, Masuda N, Iwata H. Efficacy of everolimus with exemestane versus exemestane alone in Asian patients with HER2-negative, hormone-receptor-positive breast cancer in BOLERO-2. Breast Cancer. 21, 2014, 703–714.

16. Campone M, Bachelot T, Gnant M. Effect of visceral metastases on the efficacy and safety of everolimus in postmenopausal women with advanced breast cancer: subgroup analysis from the BOLERO-2 study. Eur J Cancer. 49, 2013, 2621–2632.

17. Beck JT, Hortobagyi GN, Campone M. Everolimus plus exemestane as first-line therapy in HR, HER2 advanced breast cancer in BOLERO-2. Breast Cancer Res Treat. 143, 2014, 459–467.

18. Burris HA, III, Lebrun F, Rugo HS. Health-related quality of life of patients with advanced breast cancer treated with everolimus plus exemestane versus placebo plus exemestane in the phase 3, randomized, controlled, BOLERO-2 trial. Cancer. 119, 2013, 1908–19115.

19. Bachelot T, Bourgier C, Cropet C. 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. 30, 2012, 2718–2724.

20. Massarweh S, Romond E, Black EP. A phase II study of combined fulvestrant and everolimus in patients with metastatic estrogen receptor (ER)-positive breast cancer after aromatase inhibitor (AI) failure. Breast Cancer Res Treat. 143, 2014, 325–332.

21. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 235, 1987, 177–182.

22. Mohd Sharial MS, Crown J, Hennessy BT. Overcoming resistance and restoring sensitivity to HER2-targeted therapies in breast cancer. Ann Oncol. 23, 2012, 3007–3016.

23. Lu CH, Wyszomierski SL, Tseng LM. Preclinical testing of clinically applicable strategies for overcoming trastuzumab resistance caused by PTEN deficiency. Clin Cancer Res. 13, 2007, 5883–5888.

24. Nagata Y, Lan KH, Zhou X. PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. Cancer Cell. 6, 2004, 117–127.

25. Berns K, Horlings HM, Hennessy BT. A functional genetic approach identifies the PI3K pathway as a major determinant of trastuzumab resistance in breast cancer. Cancer Cell. 12, 2007, 395–402.

26. Miller TW, Forbes JT, Shah C. Inhibition of mammalian target of rapamycin is required for optimal antitumor effect of HER2 inhibitors against HER2-overexpressing cancer cells. Clin Cancer Res. 15, 2009, 7266–7276.

27. Andre F, Campone M, O'Regan R. Phase I study of everolimus plus weekly paclitaxel and trastuzumab in patients with metastatic breast cancer pretreated with trastuzumab. J Clin Oncol. 28, 2010, 5110–5115.

Source of Support: None declared.

Conflict of Interest: None declared.