ISSN:2348-5388

Journal of Fundamental Pharmaceutical Research
contents available at www.jfpronline.info

First global approval of Eribulin Mesylate for treatment of metastatic breast cancer

Arvind Kumar[a]*, Rahul Rama Hegde[b,c]*, Alka Lohani[b], Ankita Verma[b], Anurag Verma[b], Amrita Mishra[a], Arun K Mishra[a]

[a]Central Facility of Instrumentation, School of Pharmaceutical Sciences, IFTM University, Lodhipur- Rajput, Moradabad, 244 001, UP, India.

[b] Department Of Pharmaceutics, School of Pharmaceutical Sciences, IFTM University, Lodhipur- Rajput, Moradabad, 244 001, UP, India

[c] Quality Assurance, Lupin Ltd, Verna Industrial Estate, Verna- 403722, Goa, India

Submission Info:

Available online
01/07/2014

Corresponding Author:

Rahul Rama Hegde
Quality Assurance, Lupin Ltd,
Verna Industrial Estate,
Verna- 403722, Goa, India
Email: rahulhpharma@gmail.com

ABSTRACT: Rare marine sponges originated in deep sea are found to highly active against malignant neoplasm. Lack of plentifulness of these sponges makes them remain unused for their clinical exploration. With the expansion in developments in modern chemistry enabled to synthesize analogs similar to naturally occurring rare sponges. Eribulin mesylate (EM) is one of the synthetic analogues of halichondrin B (halB), a natural product separated from the marine sponge *Hchondria okadai*. EM is approved to treat metastatic breast cancer (MBC) chemotherapy regimens for late-stage of breast neoplasia. EM shows its pharmacologic effects by binding to the plus ends of microtubules and stops microtubule (MT) growth, without any perverse effects on microtubule shortening, by forming nonproductive tubulin aggregates. EM is the latest MT inhibitor to be approved in the USA, EU and few Asian countries. This review summarizes the milestones in the development of EM leading to its first global approval for treatment of metastatic breast cancer.

Keywords: Eribulin mesylate, Breast cancer, Tubulin, Microtubule, Halichondrin B, DNA repair.

Introduction

Metastatic breast cancer (MBC) is a serious disease affecting wide range of people across the world. Breast cancer (BC) is the leading cause of deaths

one third of 1.3 million women who diagnose as a patient with BC. Over half a million deaths occur each year[1–2]. Even in developed countries like the United States (US), as many as 30% of women diagnosed with early BC will develop distant metastatic disease that progresses to death in all but a small percent of patients [3]. Majority of BC are diagnosed at later stages in developing countries. For 5% of American patients, the disease has already progressed to stage IV when it is first diagnosed. Rate is higher among minority and poor women [4]. MBC is a malignant (cancer) tumor that commences either from the glands or the ducts of the breast. If starts from the glands, it is known as lobular carcinoma and when occurs in ducts, it is referred as ductal carcinoma. It is found specifically in women, but men can also get BC. It is the most common type of cancer among women in the US, other than the skin cancer and is the second leading cause of cancer death in women, after lung cancer [5-6]. There are several types of BCs; some of them are of rare occurrence. Sometimes a BC can be a combination of one or two types or a mixture of invasive and *in situ* cancer.

1.1. Ductal carcinoma in situ (DCIS):

This is a type of non-invasive BC. DCIS results from a disruption in the structure of the breast glandular epithelium including drop of the hollow lumen and epithelial cell proliferation in acinar units that happen via an imbalance between apoptosis and proliferation. DCIS is generally categorized by structural elucidation into five groups: comedo, cribriform, papillary, solid and micropapillary. It specifies that cancer cells are only in the ducts. They have not grown through the walls of the ducts into the tissue of the breast and thereby cannot spread to lymph nodes or other organs[7-8].

1.2. Invasive (or infiltrating) ductal carcinoma (IDC):

This is the most common type of BC. Invasive lobular carcinoma (ILC) accounts for 8–14% of all breast cancers. It originates from the milk passage (a duct) and breaks through the wall of the duct, and invades the tissue of the breast. From there it can spread (metastasize) to other parts of the body. It accounts for about 8 out of 10 invasive BC [9].

***1.3. Invasive (infiltrating) lobular carcinoma (ILC*)**: ILC is the next most popular breast malignancy after invasive ductal carcinoma (IDC). In most series, ILC composes 5–15% of all diagnosed breast cancers, whereas IDC composes 70–90%. This cancer produces in the milk glands (the lobules) and then undergoes spreading through the wall of the lobules. It can then further spread (metastasize) to other parts of the body. Around 1 in 10 invasive BCs are of this type. ILCs are obtained from minor, unvaried tumor cells with circular nuclei and fine cytoplasm that are managed in a classic single-file pattern [10].

1.4. Inflammatory breast cancer (IBC):

This is a very uncommon type of BC that accounts for about 1% to 3% of all BCs. In IBC, the cancer cells may not develop as a lump that can be perceived in the breast. They develop along the tiny channels in breast' skin. This inhibits the vessels. Usually there is no single lump or tumour present, in this type of cancer the skin of the breast turns red with warm feeling. It also may make the skin look thick. In the early stages of cancer development, inflammatory BC is often mistaken for infection. Because there is no defined lump, it may not show up on a mammogram, which may make it even harder to catch early. It has a higher chance of spreading and a worse outlook than invasive ductal or lobular cancer [11]. Various types of BCs are diagrammatically shown in figure 1.

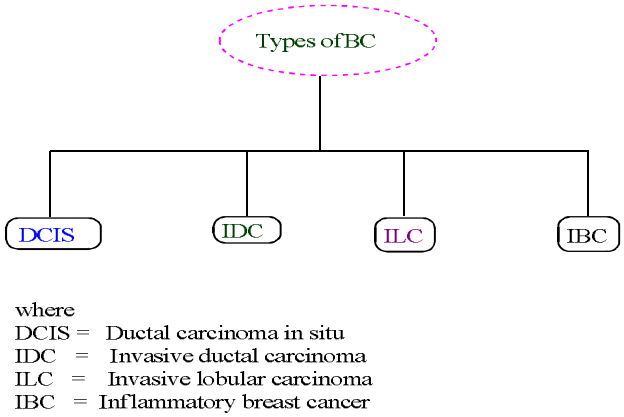


Figure: 1 diagrammatic representation of types of breast cancer

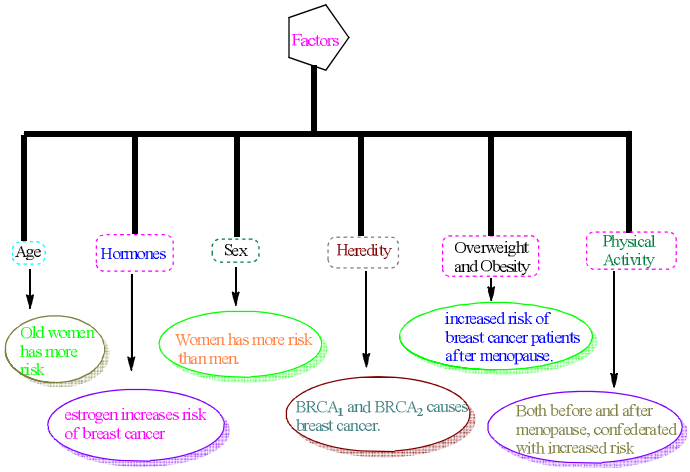


Figure: 2 diagrammatic representation factors affecting breast cancer

Lobules are the glands that cause production of milk and are connected to the nipple via ducts. Fatty, connective and lymphatic tissue also forms breast. During 2004-2008, about 83% of *in situ* cases of ductal carcinoma were diagnosed the most common type of non-invasive BC. During the same period, lobular carcinoma (11%) *in situ* BCs diagnosed. About 227,000 American women suffered from MBC in the year 2012 [12-13].

Metastatic Breast cancer (MBC) is affected by a number of major factors:

A number of factors affect the MBC and diagrammatically explained in figure 2.

1. **Age:**

Age is globally identified risk factors for BC. Younger women have less risk of BC than old one. The combined effect of a greater number of elderly women than men in most populations and the increasing prevalence of BC with age is the most likely explanation for this observation [14].

2. **Sex**:

Women have higher risk of developing BC then men. Women have more average standardized incidence rates (60.5/100,000) of breast cancer than men (1.4/100,000) in the period 1999-2009. Females have 45 times greater the average standardized incidence rates than males [15-16].

3. **Heredity:**

The autosomal dominant genes (BRC_{A1} and BRC_{A2}) are responsible for developing BC. BRC_{A1} was sympathized on chromosome 17q, ovarian cancer and BC perceptivity gene. Cloning and sequencing of BRC_{A1} disclosed *24* exons and 55^{92} nucleotides. The coding region of 130 germline mutations is announced in the Breast Cancer Information Core database [17].

4. **Hormones:**

Chances of BC increases with the increased level of estrogen but before menopause does not find any clear amalgamation with the risk of breast cancer. Decreased blood level of progesterone is amalgamation with an increased risk of BC in woman [18-19]. Raised serum levels of both estrogens and androgens speculate the risk of breast cancer after menopause [20-21]. Women in the upper quintile of estradiol or testosterone appeared the insecurity of BC to be 2 to 3 times higher than women in the lower quintile. A number of epidemiological learning incompatibly showed a confederation between serum insulin or C-peptide and the risk of breast cancer. Raised serum insulin levels and Insulin like growth factor-I however, are confederated with an increased chances of relapses in breast cancer patients [22-23].

5. **Overweight and Obesity:**

Overweight and obesity are important factors which confederated increased chances of relapses in BC patients after menopause. On adjusting serum levels of endogenous estrogens, the confederation declines markedly and it was proposed that effect of overweight by aromatization of androgens into estrogens in the adipose tissue. Before menopause, obesity proposed either no confederation or markedly declined BC chance [24-25].

6. **Life Style and Physical Activity:**

Both before and after menopause, lifestyle is confederated with increased risk of BC. Those women involve continually some physical activity and exercise declines BC risk (30% or more). There is prove that physical activity and exercise may also prevent against cancer intermittence. Daily physical activity and walking may decrease BC intermittences by 50% [26-27].Diagrammatic representation of factors affecting of breast cancer are shown in figure 2.

Hirata and Uemura, isolated halichondrin B (a natural large polyether macrolide), from a rare marine Japanese sponge, *Halichondria okadai* and reported its exquisite anticancer activity against murine cancer cells both *in vitro* and *in vivo* in 1985 [28-29].

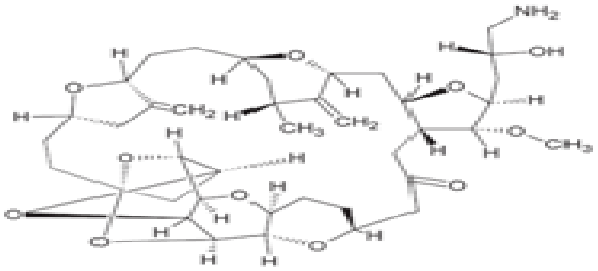
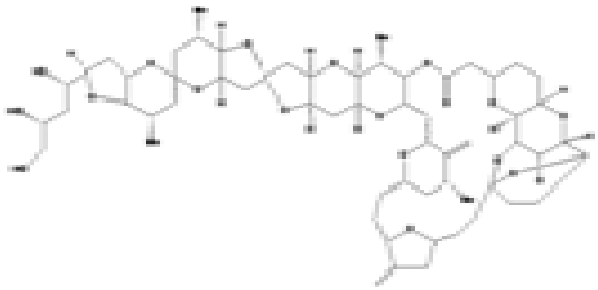
EM is extracted from the marine sponge *Hchondria okadai,* a halichondrin B analogue, a nontaxane inhibitor of microtubule dynamics. Halaven® is marketed trade name of EM. On November 15, 2010 U.S. Food and Drug Administration, gave approval to (Eisai Co.) for EM for the treatment of MBC for patients who have received at least 2 BC chemotherapeutic regimens, including an anthracycline and a taxane. Based on the results of the pivotal Phase III EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Treatment of Physician's Choice (TPC) Versus Eribulin E7389) study, EM received European Commission approval on March 17, 2011 [30]. Additionally, it received approval in Singapore [31] and in Japan [32] and market applications also have been filed in Switzerland and Canada. EM is available in 50 countries worldwide now [31]. 2-(3-Amino-2-hydroxypropyl)hexacosahydro-3-methoxy- 26-methyl-20,27-bis(methylene)11,15-18,21-24,28-triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo(3,2-i)furo(2',3'-5,6)pyrano(4,3-b)(1,4)dioxacyclopentacosin-5-(4*H*)-one is the chemical name of EM.826.0 (729.9 for free base) is its molecular weight. $C_{40}H_{59}NO_{11}\cdot CH_4O_3S$ is its empirical formula [33-34]. Some properties and features of EM are shown in table 1.

Mechanism of action

The microtubule growth is suppressed, without corresponding effects on microtubule shortening, and the formation of nonproductive tubulin aggregates occurs when EM binds to the plus ends of microtubules [18-19]. Other tubulin-targeted agents, for example taxanes, epothilones, and vinca alkaloids have different mechanism of action. To both the plus ends and along the sides of the microtubule [vinca

alkaloids (e.g., vicristine) binds] whereas, two β-tubulin subunits inside the microtubule taxanes (e.g., paclitaxel and docetaxel) and epothilones (e.g., ixabepilone) binds [28].

Table 1: Physicochemical, pharmacokinetic properties of eribulin mesylate

Features and Properties of Eribulin mesylate	
Alternative names	Halaven, E7389, ER086526, NSC707389
Class	Ketone
Mechanism of Action	Microtubule dynamics inhibitor
Route of Administration	Intravenous
Pharmacokinetic	Rapid, dose proportional absorption after intravenous administration, with steady-state plasma concentration achived in less than 1 week Approximetly 82% of drug is eliminated via faeces
Adverse events Most frequent (incidence ≥ 5%)	Neutropenia, leukopenia, and peripheral neuropathy
Chemical Name	2-(3-Amino-2-hydroxypropyl)hexacosahydro-3-methoxy- 26-methyl-20,27-bis(methylene)11,15-18,21-24,28-triepoxy-7,9-ethano-12,15-methano-9H,15H-furo(3,2-i)furo(2',3'-5,6)pyrano(4,3-b)(1,4)dioxacyclopentacosin-5-(4H)-one
Chemical structure of eribulin mesylate	
Chemical structure of halicondrin B	

Other tubulin-targeted agents, for example taxanes, epothilones, and vinca alkaloids have different mechanism of action. To both the plus ends and along the sides of the microtubule [vinca alkaloids (e.g., vicristine) binds] whereas, two β-tubulin subunits inside the microtubule taxanes (e.g., paclitaxel and docetaxel) and epothilones (e.g., ixabepilone) binds [28]. Inhibition of the formation of mitotic spindles results in irreversible mitotic block (which ultimately leads to cell cycle arrest in the G2-M phase), disruption of mitotic spindles as well as apoptosis[10]. EM is found to be a potent substrate of P-gp mediated efflux pump and it possesses an *in vitro* anticancer activity against cancerous cells that are found to be taxane-resistant due to β-tubulin mutations. It was also depicted that EM shows significant clinical effectiveness in patients suffering from taxane-resistant refractory tumors. The mechanism of action of EM is diagrammatically explained in figure 3 [35-37].

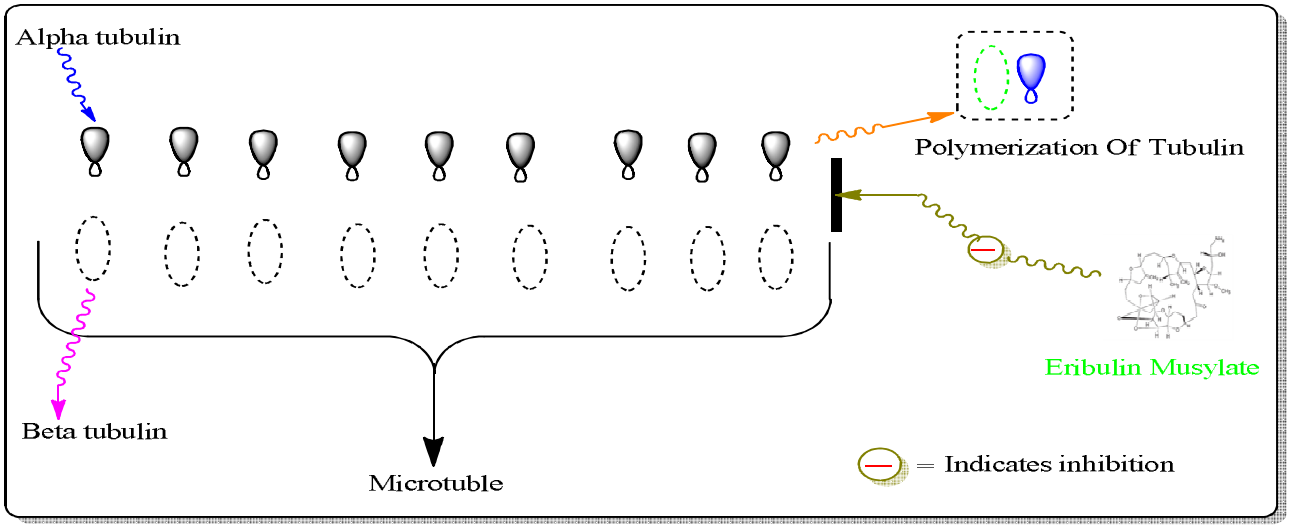


Figure 3: Mechanism of action of eribulin mesylate.

Pharmacokinetic Studies

According to FDA approval, in a dose-dependent manner with rapid distribution slow-to-moderate clearance, and slow elimination the pharmacokinetic profile of EM is linear. Plasma levels of EM are above concentrations required for *in vitro* cytotoxicity for > 1 week at the maximum tolerated dose (MTD), [19] EM is rapidly distributed via intravenous route of administration, with a mean distribution half-life of about 0.43 hours. In a Phase I study of 21 patients the mean (standard deviation) volume of distribution with advanced solid tumors was found to be 47.8 (10.14) L/m^2 at the 1-mg/m2 dose level and 87.4 (49.32) L/m^2 at the 2-mg/m2 level. The mean AUC (area under the curve) time curve was found to be 0.486 to 0.653 (hour) (g/mL) at 1 mg/m2 dose level, 0.856 (hour) (g/mL) at 1.4-mg/m2 dose level, and 1.842 (hour) (g/mL) at 2-mg/m^2 dose level, as revealed by various authors. P450 3A4 isoenzyme (CYP3A4) is responsible for the metabolism of EM and has shown insignificant inhibitory effects on CYP1A, CYP2C9, or CYP2C196. EM neither induce CYP3A4 nor inhibit CYP2D6 or CYP2E11 [38]. A total of about 82% of EM is found to be eliminated via faeces, 9% through urine, 88% and 91% of which contains the unchanged form of EM, respectively [35-38]. EM has demonstrated activity both *in vitro* and *in vivo*, with a relatively wide therapeutic window and favorable pharmacokinetics. EM was active at

nanomolar concentrations against lung, ovary, prostate, colon, and also breast cancer cell lines, including MDA-MB-435, where EM was more potent as compared to either vinblastine or paclitaxel [39]. Notably, EM demonstrated full activity in ovarian cell lines with β-tubulin mutations resistant to paclitaxel [40]. It was also demonstrated in another study, about the β III tubulin expression levels appeared to correlate with sensitivity to EM, and this relationship was not sufficiently proven to be used as a biomarker strategy in the clinic [41]. Human xenograft studies of a range of tumor types *in vivo*, including three BC models, and demonstrated activity at doses of 0.05–1.0 mg/kg. EM was found to be more potent with striking activity against MDA-MB-435 BC xenografts than paclitaxel and vinca alkaloids [39]. Available preclinical model indicates intermittent dosing was less toxic and more effective than daily dosing [42]. EM appeared to cause less neurotoxicity. EM manifests less functional and morphological damage, than paclitaxel in mice [43].

Clinical studies with Eribulin mesylate

Clinical Phase-1 trials

California cancer consortium (CCC) was responsible for conducting the first phase trial at the on patients with refractory or advanced solid tumors [44]. It followed a designing of rapid titration with pharmacokinetic (real-time) analysis to guide dose escalation [45]. Neutropenia was ought to be the most commonly reported dose-limiting toxicity (DLT). Two DLTs were reported at 2.0 mg/m^2 (grade 3 febrile neutropenia [n = 1]; grade 4 neutropenia [n = 1]. Hypoglycemia, hypophosphatemia, and fatigue are the serious non-hematologic related toxicities. The maximum tolerated dose of EM was evaluated to be 1.4 and 1.0 mg/m^2 in various research reports as observed in studies dosing on days 1, 8, and 15 of a 28-day cycle. The resulted MTD was found to be 2.0 mg/m^2 on dosing on day 1 of a 21-day cycle, whereas dosing on days 1 and 8 of a 21-day cycle led to a maximum tolerated dose of 1.4 mg/m^2 [38,46].

Clinical phase-2 trials

The phase II and III trials of EM continued with the bolus 1.4 mg/m^2/week, on days 1, 8, and 15 of a 28-day cycle schedule as recommended by the CCC study [44]. However due to progressive neutropenia in many patients on day 15 leading to change in dosing frequency or omission, treatment schedule was modified to days 1 and 8 of a 21-day cycle which emerged to be more favorable **[**47-48**].**

A single-arm, open-label, multicenter phase II trial study consisted of 103 patients with MBC. Anthracycline and taxane (median of 4 chemotherapy regimens) were administered to patient previously. On 1st, 8th, and 15th day of a 28-day cycle EM (1.4 mg/m^2) was initially administered in the form of 2–5 min intravenous infusion. On 15th day, however, many patients were observed with sudden outbreak of neutropenia which precluded EM administration. The objective response rate (ORR) includes the primary endpoint. More than half of patients about, 54% had shown an Eastern Cooperative Oncology Group (ECOG) performance status of 1 at base line. Patients observed in the 28th day cohort, received a median of 2.5 cycles of therapy as compared with a median of four cycles in the 21st day cohort. The median progression-free survival (PFS) and overall survival (OS) were found to be 2.6 and 9.0 months, respectively[49].

Clinical phase-3 trials

EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) was first trial which is used in this study. In this study, on days 1 and 8 of a 21 day cycle or treatment with physician's choice (TPC) the EM 1.4 mg/m^2 over 2-5 minutes were given to MBC woman's (previously treated with two to five prior chemotherapy regimens including an anthracycline and a taxane). The

EMBRACE trial (NCT00388726) was considered to be a phase III study of EM. The primary endpoint was depicted to be OS reporting a median overall survival of 13.1 months for patients administered with EM and 10.7 months for patients in case of TPC arm (hazard ratio 0.81; 95% CI = 0.66–0.99, p = 0.04). For those treated with TPC, the resulted ORR was found to be 12.2% and 4.7% respectively. The median PFS was evaluated to be 3.7 and 2.2 months treated with EM and TPC, respectively (HR 0.87; 95% CI = 0.71–1.05; p = 0.14 [49, 50].

Phase 3 (study 301)

A two parallel-arm, open-label, randomized, multicenter phase III trial study consists of 1,102 volunteers with MBC. Inclusion criteria included women (≥18 years) with locally recurrent or MBC previously treated with 2–5 prior chemotherapies including an anthracycline and a taxane. In this study, on days 1 and 8 of a 21 days cycle EM (1.4 mg/m^2/day) was intravenously administered. On days 1-14 of a 21 days cycle capecitabine (2.5 g/m^2/day) was orally administered and both drugs compared to each other. This has found it's the approval in Europe and the United States. Treatment-related adverse events of interest for EM were neutropenia (54.2%), hand-foot syndrome (0.2%), alopecia (34.6%), leukopenia (31.4%) and diarrhea (14.3) and for capecitabine. neutropenia (15.9%), hand-foot syndrome (45.1%), alopecia (4.0%), leukopenia (10.4%) and diarrhea (28.4). In all patients 755 were HER2-negative and 284 were HER2-positive. The median progression-free survival (PFS) and overall survival (OS) of EM were found to be 15.9 and 4.1 months, respectively. The PFS and OS of capecitabine were obtained 14.5 and 4.2 months [51].

Clinical phase-4 trials (Post Marketing Surveillance)

This trial has conducted in Korea, started date June 2013. A single-arm, open-label, non randomized, multicenter phase IV trial study consists only female patients (20 Years and older) with MBC, whose previously treated by two to five prior chemotherapy regimens including an anthracycline and a taxane for advanced disease. In this study, on days 1 and 8 of a 21 day cycle or treatment of EM 1.4 mg/m^2 over 2-5 minutes for study to determine the safety of EM. Level of serum creatinine ≥ 2.0mg/dl,creatinine clearance ≥ 40 ml/min (Calculated by Cockcroft and Gault method), absolute neutrophil count (ANC) ≥1.5 x 10^9 /L, hemoglobin ≥10.0 g/dl, stable sensory neuropathy ≤ grade2. All of these factors are included in incision criteria. Enrollment has been completed and estimated study completion and reporting date is July 2016 [52]. The outcome of this ongoing study will put more light on newer issues relating to the adverse effects of EM on long term use in large range of population which is rarely possible in the basic phases of clinical trial phase I, II respectively.

Current antiproliferative profile of EM:

In *in vitro* antiproliferative activity, EM was evaluated to inhibit the growth of human cancer cell lines having IC_{50} value in range from sub to low nmol/L IC_{50} values (0.09–9.5 nmol/L), including DU 145 and that of LNCaP prostate cancers, U937 histolytic lymphoma, FaDu pharyngeal squamous cell carcinoma (head and neck cancer), A2780/1A9 ovarian cancer, MES-SA uterine sarcoma, HL- 60 promyelocytic leukemia, and LOX melanoma, MDA-MB-231, -435, -468 and HCC1806 breast cancers, HT-29, COLO 205 and DLD-1 colon cancers, H23, H441, H520 and H522-T1 non-small cell lung carcinomas (NSCLC), NCI-H82 small cell cancer [53-54]. In *in vivo* antitumor activity studies using subcutaneous xenograft models in athymic mice depicted tumor regressions, remissions and an enhanced lifespan at dose levels below the maximum tolerated dose (MTD) [55,56]. *In vivo* anticancer activity of EM in MDA-MB-435, COLO 205 and LOX cell lines (in NIH: OVCAR-3 model, significant only) are observed to possess much lower values (0.05–1 mg/kg i.v. or i.p.) as compared to paclitaxel, run at empirically determined MTD

levels. Treatment with 0.25–1.0 mg/kg dose of EM mesylate in the MDA-MB-435 model showed actual regression of measurable tumors by day 14, >95% inhibition at day 42 with no evidence of cytotoxicity. EM (0.05 mg/kg) inhibited the tumor growth by the rate of about 78% on day 17th in LOX melanoma model and higher doses resulted in complete tumor suppression. EM was observed to be more potent in NIH: OVCAR-3, COLO 205, LOX and MDA-MB-435 models by 20, 40, 50 and 100 times respectively as compared to paclitaxel running at MTD levels [53, 57].

Known adverse events associated with EM:

In patients receiving EM, neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation are most common adverse reaction. Grade 3 or 4 adverse effects that occurred in about 5% of patients were more common with EM than with physician's choice and include neutropenia, leukopenia, and peripheral neuropathy. Grade 3 and 4 side effects include asthenia/fatigue. 52% of patients in EMBRACE, 45% of which were grade 3 or 4 (compared with 30% of patients in the physician's choice group, 21% of which were grade 3 or 4) experience neutropenia (the most common adverse event associated with EM) [12,33]. The most common adverse reaction which express result in discontinuation of therapy with EM was peripheral neuropathy was very rarely observed. Various adverse reactions neurotoxicity such as peripheral neuropathy, motor neuropathy, sensory neuropathy, myalgia/arthralgiac, nervous system disorders, dizziness, dysgeusia, Headache was caused by EM [47, 53].

Management of BC according to new treatment strategies and EM:

Recent published reports on the management of breast cancer observed both in patients suffering from metastatic disease and in patients suffering with triple negative MBC or human epidermal growth factor receptor-2 (HER2)-positive tumors, Anti-HER2 therapies are considered to be an essential part in the BC management. EMBRACE study; have been demonstrated for safety and efficacy of this agent in last stages of MBC involved the study on 762 patients with locally recurrent or metastatic disease. Median of four agents including an anthracycline and a taxane were used for treating patients. On days 1 and 8 of a 3-week cycle or a treatment of their physician's choice EM, 1.4 mg/m^2 were given to patients randomly. In 1-year the survival rates were 53.9% in EM treated patients and 43.7% in patients receiving other therapies. A humanized monoclonal antibody known as bevacizumab is employed against vascular endothelial growth factor (VEGF)-A. To improve progression-free survival as well as the response rates, a combination of bevacizumab and chemotherapy have been shown. Bone loss in BC patients is caused by chemotherapy and bone metastasis; hence bone-conserving therapies are attracting increasing attention in the management of BC. FDA has approved denosumab in November 2010 [38]. It is a human monoclonal antibody used against receptor activator of nuclear factor kB ligand (RANKL), which was found to be effective for the treatment of bone metastasis [58]. The efficacy of this therapeutic agent has been compared with zoledronic acid recently, in a randomized, double-blind study in patients with advanced BC and bone metastasis [59]. Early distance metastasis and brain metastasis get developed in patients with triple negative BC than those of other phenotypes. Lack of effective therapy for treating triple-negative BC is considered to be a major therapeutic challenge across the globe. Use of DNA repair mechanism plays a key role in therapeutic targeting in case of triple negative BC [60-61]. Poly (ADO ribose) polymerase (PARP) is an important target and it is potentially useful in a DNA repair mechanism. PARP inhibitors have been shown to be effective in killing breast and ovarian cancer cells that lack wild – type BRCA or BRCA genes. PARP was found to repair single-strand DNA breaks through the base excision repair pathway [62].

Conclusion and future prospects in the management strategies of BC:

A combination of anti-HER2 therapies with agents directly targeted, such as mTOR and PI3K inhibitors are currently being evaluated in various clinical trial studies. The ALTTO study is working in this aspect to demonstrate the benefits of combination or sequential treatment with trastuzumab and the dual tyrosine kinase inhibitor lapatinib [60]. There are other clinical trials, such as GEPARQ unto and Neo ALTTO, which are evaluating the use of lapatinib as neoadjuvant therapy in HER2-positive patients [58]. According to the Neo ALTTO study, a woman who has been suffering from HER2-positive primary breast cancer were administered with lapatinib with paclitaxel, trastuzumab with paclitaxel or concomitant lapatinib and trastuzumab with paclitaxel [63].

BC is gaining prominent importance across the globe nowadays, as its growth rate is enhancing day by day. Thereby, various researches have been made in the development of new therapies and strategies by which existing treatments can be optimized in aspect of improving their therapeutic efficacy. Thus, it was concluded that phase II trial showed that EM is a novel drug and possessed therapeutic activity in the treatment of MBC in patients who have been previously administered with a median of four chemotherapy regimens that includes an anthracycline and a taxane. EM depicted a manageable tolerability profile when administered in the form of short IV infusion on day 1st and 8th of a 21-day cycle. These results emphasizes mainly on the additional clinical development of EM for the efficacious and safe treatment of MBC.

Acknowledgement:

Authors are grateful to Prof. R M Dubey, Vice Chancellor of IFTM University for providing necessary facilities for this research work.

Declaration of Interest:

The authors declare that there is no conflict of interests regarding the publication of this article.

References

1. Parkin DM, Bray F, Ferlay J. Global cancer statistics, 2002, CA. Cancer Journal Clinicians, 2005; 55: 74-108.

2. Stewart BW, Kleihues P. World Cancer Report (World Health Organization), Lyon: IARCC Press, 2003.

3. Shaughnessy OJ. Extending survival with chemotherapy in metastatic breast cancer. Oncologist, 2005; 10: 20-29.

4. Mayer M. Lessons learned from the metastatic breast cancer community. Seminars in Oncology Nursing, 2010; 26(3):195-202.

5. Alison MR. Cancer. Encyclopedia of life sciences, Nature Publishing House, 2001; 108.

6. The patient education institute, Inc. X-Plain Patient Education, Breast cancer, 1-10. http:/www.nlm.nih.gov./medlineplus/tutorials/breast.(www.X-Plain.com)

7. Myong JH, Choi BG, Kim SH, Kang BJ, Lee A, Song BJ. Imaging features of complex sclerosing lesions of the breast. Ultrasonography. 2014;33(1):58-64

8. Debnath J. Mills KR, Collins NL, Reginato MJ, Muthuswamy SK, Brugge JS. The role of apoptosis in creating and maintaining luminal space within normal and oncogene-expressing mammary acini. Cell, 2002; 111: 29–40.

9. Arpino G. Bardou VJ. Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res. 2004; 6(3): R145-156.

10. Albayrak ZK. Onay HK. Karatağ GY. Karatağ O. Invasive lobular carcinoma of the breast: mammographic and sonographic evaluation. Diagn Interv Radiol. 2011; 17(3): 232-8.

11. Bazzocchi M, Facecchia I, Zuiani C, Puglisi F, Di Loreto C, Smania S. Diagnostic imaging of lobular carcinoma of the breast: mammographic, ultrasonographic and MR findings. Radiol Med. 2000; 100(6): 436-43.

12. Ghumare SS, Cunningham JE. Breast cancer trends in India residents and emigrants portend and emerging epidermic for India, Asian Pac J Cancer Prev. 2007; 8(4):507-12.

13. Bodapati SL, Babu GR. Oncologist perspectives on breast cancer screening in India- results from a qualitative study in Andhra Pradesh. Asian Pac J Cancer Prev. 2013; 14(10):5817-23.

14. Stuart OJ. Bathsheba's Breast: Women, Cancer and History. Baltimore: The Johns Hopkins University Press, pp.199–200, 2002.

15. Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN. Breast carcinoma in men: a population-based study. Cancer.2004; 101(1):51-7.

16. Sipetic-Grujicic S, Murtezani Z, Ratkov I, Grgurevic A, Marinkovic J, Bjekic M, Miljus D. Comparison of male and female breast cancer incidence and mortality trends in Central Serbia. Asian Pac J Cancer Prev. 2013; 14(10):5681-5.

17. Malone KE, Daling JR, Thompson JD, O'Brien CA, Francisco LV, Ostrander EA. BRCA1 mutations and breast cancer in the general population: analyses in women before age 35 years and in women before age 45 years with first-degree family history. JAMA, 1998; 279(12):922-9.

18. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. N Engl J Med. 2006; 354(3):270-82.

19. Nisker JA, Siiteri PK. Estrogens and breast cancer. Clin Obstet Gynecol. 1981; 24(1): 301-22.

20. Kaaks R, Rinaldi S, Key TJ. et al. Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. Endocr Relat Cancer. 2005; 12(4):1071-82.

How to cite this article: Kumar A. 2014. First global approval of Eribulin Mesylate for treatment of metastatic breast cancer. J. Fundam. Pharm. Res., 2(1): 7-21

21. Key T, Appleby P, Barnes I, Reeves G. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst. 2002 Apr 17; 94(8):606-16.

22. Micheli A, Muti P, Secreto G, Krogh V, Meneghini E, Venturelli E, Sieri S, Pala V, Berrino F. Endogenous sex hormones and subsequent breast cancer in premenopausal women. Int J Cancer. 2004; 112(2): 312-8.

23. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, Hartwick W, Hoffman B, Hood N. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol. 2002; 20(1): 42-51.

24. Lahmann PH, Hoffmann K, Allen N, van Gils CH, Khaw KT. et al,. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer. 2004 ;111(5): 762-71.

25. Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C. et al. ,. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst. 2003;95(16):1218-26.

26. Cleary MP, Maihle NJ. The role of body mass index in the relative risk of developing premenopausal versus postmenopausal breast cancer. Proc Soc Exp Biol Med. 1997; 216(1):28-43.

27. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. JAMA. 2005; 293(20): 2479-86.

28. W. Bergmann and R. J. Feeney, "The isolation of a new thymine pentoside from sponges. J. Am. Chem. Soc. 1950; 72(6): 2809–10.

29. Gibbs R. Top-level Advisory Committee on Defense Scientific Research being set up . . . Action still awaited on creation of central organization to receive and evaluate research proposals of potential defense value. Chem. Eng. News. 1951; 29 (11): 982.

30. Pean E, Klaar S, Berglund EG, Salmonson T, Borregaard J, Hofland KF, Ersbøll J, Abadie E, Giuliani R, Pignatti F. The European medicines agency review of eribulin for the treatment of patients with locally advanced or metastatic breast cancer: summary of the scientific assessment of the committee for medicinal products for human use. Clin Cancer Res. 2012; 18(17): 4491-7

31. Scarpace SL. Eribulin mesylate (E7389): review of efficacy and tolerability in breast, pancreatic, head and neck, and non-small cell lung cancer. Clin Ther. 2012; 34(7):1467-73.

32. Cigler T1, Vahdat LT. Eribulin mesylate for the treatment of breast cancer. Expert Opin Pharmacother. 2010; 11(9):1587-93.

How to cite this article: Kumar A. 2014. First global approval of Eribulin Mesylate for treatment of metastatic breast cancer. J. Fundam. Pharm. Res., 2(1): 7-21

33. Halaven (package insert). Woodcliff Lake, NJ: Eisai Inc. 2010.http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=31ce4750-ded5-4a0b-95e9-f229fa6bc822. Retrieved 19/06/2014.

34. Pal DK, De T, Baral A. Eribulin mesylate: A drug for treatment of advanced metastatic breast cancer (MBC) with new treatment strategies. Int J Pharm Sci. 2013; 3(3): 244-47.

35. McBride A, Butler SK. Eribulin mesylate: a novel halichondrin B analogue for the treatment of metastatic breast cancer. Am J Health Syst Pharm. 2012; 69(9): 745-55.

36. Swami U, Chaudhary I, Ghalib MH, Goel S. Eribulin—A review of preclinical and clinical studies. Crit Rev Oncol Hematol. 2012; 81(2): 163–84.

37. Cortes J, Vidal M. Beyond taxanes: the next generation of microtubule-targeting agents.
Breast Cancer Res Treat. 2012; 133(3):821-30

38. Scarpace SL. Eribulin mesylate (E7389): Review of Efficacy and Tolerability in Breast, Pancreatic, Head and Neck, and Non–Small Cell Lung Cancer. Clin Ther. 2012; 34(7):1467-73.

39. Towle MJ1, Salvato KA, Budrow J, Wels BF, Kuznetsov G, Aalfs KK, Welsh S, Zheng W, Seletsky BM, Palme MH, Habgood GJ, Singer LA, Dipietro LV, Wang Y, Chen JJ, Quincy DA, Davis A, Yoshimatsu K, Kishi Y, Yu MJ, Littlefield BA. In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. Cancer Res. 2001; 61(3):1013-21.

40. Kuznetsov G, Dyke KT, Yu M, Littlefield B. Antiproliferative effects of halichondrin B analog eribulin mesylate (E7389) against paclitaxel-resistant human cancer cells in vitro
AACR Meeting Abstracts 2007 2007: C58

41. Agoulnik S, Kuznetsov G, Tendyke K, Parent LA, Marsh JP, Twine N, Renshaw FG, Silberman S, Littlefield BA. Sensitivity to halichondrin analog E7389 and hemiasterlin analog E7974 correlates with β III tubulin istotype expression in human breast cancer cell lines. J Clin Oncol (Meeting Abstracts) 2005; 23(16) suppl 2012

42. Dabydeen DA, Burnett JC, Bai R, Verdier-Pinard P, Hickford SJH, Pettit GR, Blunt JW, Munro MHG, Gussio R, Hamel E. Comparison of the Activities of the Truncated Halichondrin B Analog NSC 707389 (E7389) with Those of the Parent Compound and a Proposed Binding Site on Tubulin. Mol Pharmacol 2006; 70(6): 1866-75.

43. Smith JA, Wilson L, Azarenko O, Zhu X, Lewis BM, Littlefield BA, Jordan MA. Eribulin binds at microtutuble ends to a

single site on tubulin to suppress dynamic instability, Biochemistry, 2010; 49(6): 1331-7.

44. Synold TW, Morgan RJ, Newman EM, Lenz HJ, Gandara DR, Colevas AD, Lewis MD, Doroshow JH. A phase I pharmacokinetic and target validation study of the novel anti-tubulin agent E7389: a California Cancer Consortium trial. J Clin Oncol (Meeting Abstracts) 2005; 23(16) suppl 3036

45. Zhang ZY, King BM, Pelletier RD, Wong YN. Delineation of the interactions between the chemotherapeutic agent eribulin mesylate (E7389) and human CYP3A4. Cancer Chemother Pharmacol. 2008; 62(4): 707-16

46. Mukohara T, Nagai S, Mukai H, Namiki M, Minami H. Eribulin mesylate in patients with refractory cancers: a Phase I study. Invest New Drugs. 2012; 30(5): 1926-33.

47. Cortes J, Vahdat L, Blum JL, Twelves C, Campone M, Roché H, Bachelot T, Awada A. et al. Phase II study of the halichondrin B analog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine. J Clin Oncol. 2010; 28(25): 3922-8.

48. Vahdat LT, Pruitt B, Fabian CJ, Rivera RR, Smith DA, Tan-Chiu E et al., Phase II study of eribulin Mesylate, a halichondrin B analog, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2009; 27(18): 2954-61

49. Cortes J, Montero AJ, Glück S. Eribulin mesylate, a novel microtuble inhibitor in the treatment of breast cancer, Cancer Treat Rev. 2012; 38(2): 143-51

50. Montero AJ, Escobar M, Lopes G, Glück S, Vogel C. Bevacizumab in the treatment of metastatic breast cancer: friend or foe?. Curr Oncol Rep. 2012; 14(1):1-11.

51. PHASE III study (study 301) results of anticancer agent halaven® versus capecitabine in locally advanced or metastatic breast cancer presented at 2012 sabcs.
http://www.eisai.com/news/news201281.html

52. Eribulin mesylate phase IV clinical trial in korean patients with metastatic or locally advanced breast cancer, http://clinicaltrials.gov/show/NCT01961544. Retrieved on 03.02.2014.

53. Product information, USA, Eisai Inc
http://us.eisai.com/wps/wcm/connect/Eisai/Home/Our+Products/

54. National Cancer Institute, Division of cancer treatment and diagnosis–featured agents.
http://dctd.cancer.gov/FeaturedAgents/pdfs/E7389SolicitationMarch 2005; pdf.

55. Ludueña RF, Roach MC, Prasad V, Pettit GR. Interaction of halichondrin B and

homo halichondrin B with bovine brain tubulin, Biochem Pharmacol. 1993 Jan 26; 45(2):421-7.

56. Jordan MA, Wilson L. Microtubules as a target for anticancer drugs, Nat Rev Cancer. 2004; 4(4): 253-65.

57. Swami U, Chaudhary I, Ghalib MH, Goel S. Eribulin— a review of preclinical and clinical studies, Crit Rev Oncol Hematol. 2012; 81(2): 163-84.

58. Perez EA. New treatment strategies in the management of breast cancer, EJC Suppl, 2011; 9(2): 22-29.

59. Brufsky AM, The evolving role of bone-conserving therapy in patients with breast cancer, Semin Oncol. 2010; 37 Suppl 1:S12-9.

60. Hines SL, Vallow LA, Tan WW, McNeil RB, Perez EA, Jain A. Clinical outcomes after a diagnosis of brain metastases in patients with estrogen- and/or human epidermal growth factor receptor 2-positive versus triple-negative breast cancer. Ann Oncol. 2008; 19(9): 1561-5.

61. Helleday T, Petermann E, Lundin C, Hodgson B, Sharma RA. DNA repair pathways as targets for cancer therapy. Nat Rev Cancer. 2008; 8(3): 193-204.

62. Lal P, Tan LK, Chen B. Correlation of HER-2 status with estrogen and progesterone receptors and histologic features in 3,655 invasive breast carcinomas. Am J Clin Pathol. 2005; 123(4): 541-6.

63. Pal D, Banerjee S, Ghosh AK. Dietary-induced cancer prevention: An expanding research arena of emerging diet related to healthcare system. J Adv Pharm Technol Res. 2012; 3(1): 16-24.

How to cite this article: Kumar A. 2014. First global approval of Eribulin Mesylate for treatment of metastatic breast cancer. J. Fundam. Pharm. Res., 2(1): 7-21