REVIEW ARTICLE

Impact of Ado-trastuzumab Emtansine Therapy in Human Epidermal Growth Factor Receptor 2 Positive Metastatic Breast Cancer: A Recent Survey

Kumar Arvind, Porwal Mayur, Rastogi Vaibhav, Mishra K. Arun

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, IFTM University, Moradabad, Uttar Pradesh, India

Abstract

Recent estimate revealed that in the year 2012, about 227,000 American women suffered from metastatic breast cancer (mBC). The U.S. Food and Drug Administration (FDA) have approved ado-trastuzumab emtansine (T-DM1) on 22 February 2013 for the treatment of human epidermal growth factor receptor (HER2)-positive mBC who has previously been treated with trastuzumab and a taxane. T-DM1 received the European Commission approval on November 2013 based on results from the pivotal Phase III EMILIA trial and Switzerland is the first country which has the marketing permission for T-DM1 in Europe. In September 2013, It received marketing approval in Japan based on results from a Japanese Phase II trial and the EMILIA Phase III trial and also approved by Health Canada. T-DM1 is an antibody-drug conjugate (ADC). ADC consists of monoclonal antibody trastuzumab, which covalently linked with DM1 (cytototoxin, microtubule inhibitor) by mitotic checkpoint complex (MCC) linker. The ADC delivers the toxin specifically to tumor cells. DM1 binds to tubulin, and it disrupts microtubule network in the cell. Cell cycle arrest and apoptotic cell death were occurred. In clinical trials, patients (991) were randomly assigned in a 1:1 ratio to kadcyla or lapatinib plus capecitabine. The recommended dose is 3.6 mg/kg every 3 weeks (21-day cycle).

Key words: Ado-trastuzumab emtansine, antibody-drug conjugate, DM1, human epidermal growth factor receptor 2 positive metastatic breast cancer, kadcyla, linker mitotic checkpoint complex, overall survival, progression-free survival, TD1

INTRODUCTION

Breast cancer (BC) is main cancer seen in women of various developed and developing countries across the globe. BC is the most important reason of cancer deaths in females between 20 and 59 years.[1] About 39,620 women were died due to BC in 2013 and approximately 2,240 men were identified with BC, and out of this, 410 men were died in 2013. Metastatic BC (mBC) is the proliferation of cancer cells from the actual site where cancer was first occurred in the body. It is connected with expanded severity and is chiefly incurable. The median survival for a woman with this form of BC is about 2 years.[2] In the United States, according to a survey report of 2012, BC was the most common cancer, about 227,000 American women suffered from mBC. Ductal carcinoma and lobular carcinoma are two most common types of BC. About 1 of every 10 women BC has lobular carcinoma.[3,4] Each year about 70,000 persons in Europe were diagnosed with advanced BC, of whom approximately one in five will have Human epidermal growth factor receptor (HER2)-positive disease.[5] In Canada, BC is the preponderance ordinary cancer diagnosed in women. A rating of 26% of all cancer cases, BC is the second leading reason of death in women. Approximately, 65 women are diagnosed with BC every day and every week, and it declares the lives of 100 Canadian women every week.[2] BC may be affected by various factors [Table 1 and Figure 1].

Address for correspondence:
Arvind Kumar, Faculty of Pharmacy, IFTM University, Lodhipur-Rajput, Moradabad - 244 001, Uttar Pradesh, India. Phone: +91-9759583231.
E-mail: AKarvindsr01@gmail.com

Received: 10-08-2016
Revised: 28-08-2016
Accepted: 07-09-2016

Table 1: Factors affecting breast cancer

Risk factors	Description
Age	Age is a crucial factor for breast cancer. It has been found that aged women have a maximum tendency of breast cancer than younger.[6,7] 79% of novel cases and 88% of breast cancer deaths occurred in women 50 years of age and older. The middle age at the moment of breast cancer diagnosis was 61 years for the period of 2006-2010[8]
Sex	In various countries, it has been found that the number of breast cancer patients is much more in women than men. In 1999-2009, women have more usual normalized occurrence rates approx 60.5/100,000 of breast cancer than men 1.4/100,000. Males have 45 times lesser the average normalized occurrence rates than females[7,9]
$BRCA_1$ and $BRCA_2$	$BRCA_1$ and $BRCA_2$ are autosomal dominant genes which play a very important role to cause breast cancer.[7,10] It is expected that 5-10% of breast cancer cases effect from BRCA1 and BRCA2, including inherited mutations. It is estimated that about 15%-20% of breast cancers occurs due to BRCA1 or BRCA2 gene mutations, 44% and 78% of women with BRCA1 mutations and between 31% and 56% of women with BRCA2 mutations will increase breast cancer[11-14]
Dietary factors	Alcohol- Excess drinking cause MBC.[15] It has been proved that alcohol utilization enhances the danger of breast cancer in women (about 7%-12% for each 10 g of alcohol drink/day). The enhanced danger of breast cancer is dose-dependent, and alcohol increases this risk by rising androgen and estrogen intensity. Alcohol consumption has a good relationship with raised danger for ER+than ER- breast cancers[16-21] Fat intake- low fat intake decreases the risk of mBC[22] Specific dietary fatty acids- higher level of monosaturated fatty acids (oleic acid) in the erythrocyte membranes of postmenopausal women caused mBC Calcium- cancer prevention study II Nutrition cohort concluded 20% lower risk of breast cancer with 1250 mg of calcium intake Vitamin D- reduces the risk of breast cancer
Obesity and lack of exercise	It has been found that obesity increased risk of developing breast cancer. Obesity associated raised the possibility of relapses in breast cancer patients behind menopause. It is proposed that the danger of breast cancer is about 2 times superior in obese women compared to women who are normal weight. It has been found by a large meta-analysis that in the middle of women ages 40-49, the threat of increasing breast cancer was about 26% lower in obese women than in lean women. Those women do not engage constantly a number of physical actions and exercise increases breast cancer hazard approximately 30% or more. There is proof that lack of exercise increased the tendency of breast cancer.[7,23,24]
Hormones	Increased levels of progesterone have the tendency to decrease the risk of breast cancer, but increased levels of estrogen hormone increased risk of breast cancer.[25,26] Many epidemiological learning incompatibly demonstrated amalgamation flanked by serum insulin or C-peptide and the risk of breast cancer. Elevated serum insulin intensity and Insulin-like growth factor-I are associated with a raised possibility of relapses in breast cancer.[7]
Tobacco	According to American Cancer Society researchers, It is estimated that those women who never smoked had a 12% lower danger of breast cancer than other women.[27]

Non-Hispanic white women have higher incidence rates of BC compared to African American women. Figure 2 explains BC incidence and death rates by race and ethnicity during 2004-2008 and 2003-2007.

BC incidence and death rates by race and ethnicity during the most recent period (2006-2010) is presented in Figure 3.

The epidermal growth factor receptor is a prototype compound of the category I superfamily of receptor tyrosine kinases (RTKs), which consists HER1, HER2, HER3, and HER4. All compounds have a ligand-binding region, a single membrane-spanning region and a cytoplasmic intracellular tyrosine-kinase-containing domain. HER2 is a transmembrane RTK that is part of a complex signal transduction network involved in cell differentiation, proliferation, and survival. HER2 is expressed in normal epithelial tissues at relatively low levels in healthy adults, but it is overexpressed in approximately 20% of tumors from patients with positive mBC. In this mBC, the cancer cells make much of a protein known as HER2/neu. In U.S, it has been found that the maximum numbers of mBC patients are HER2-positive because cancer cells display abnormally high numbers of HER2 proteins on their surface.

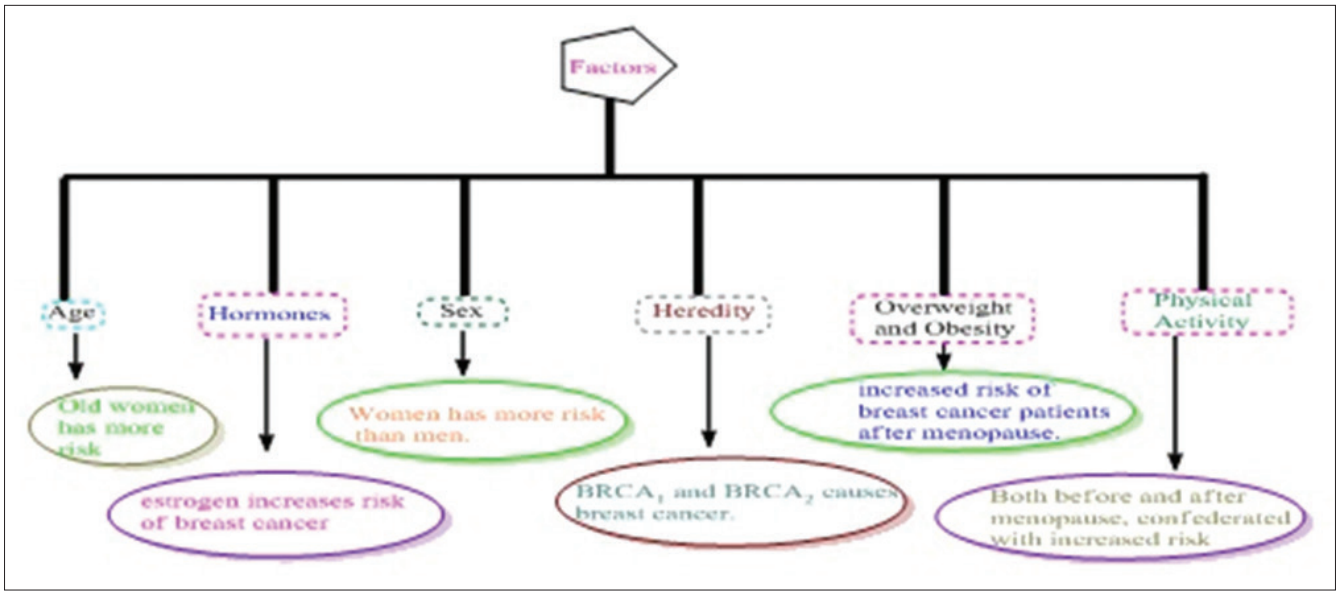

Figure 1: Factors affecting breast cancer[7]

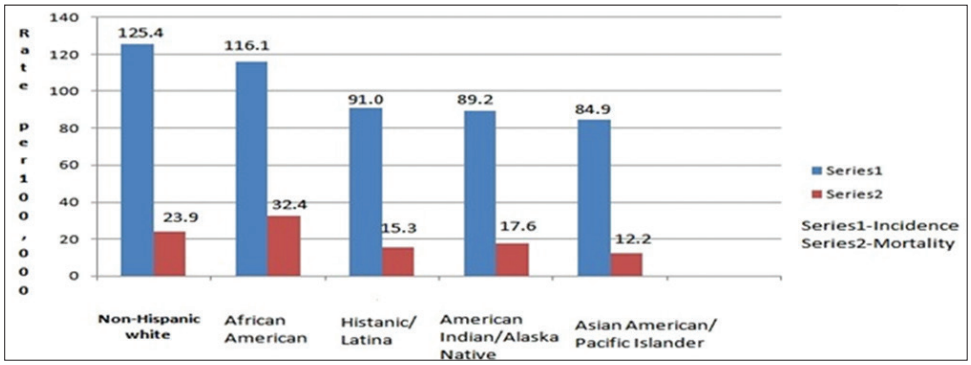

Figure 2: Female breast cancer incidence (2004-2008) and mortality (2003-2007) rates by race and ethinity[27,28]

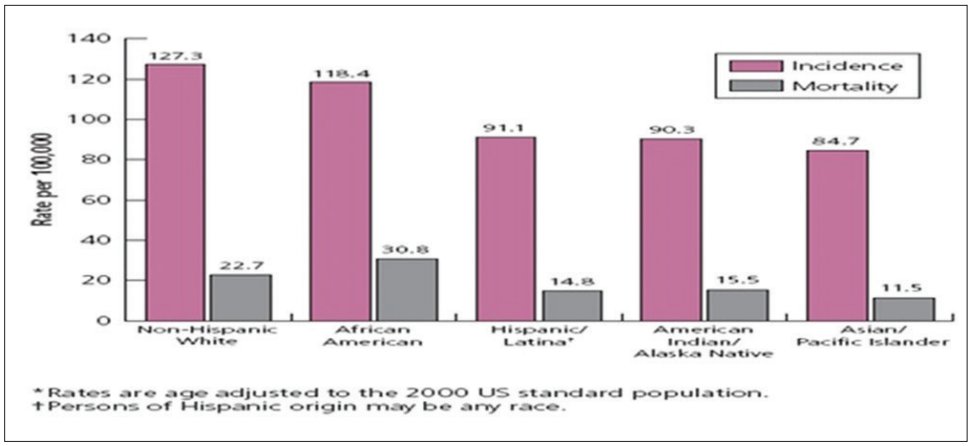

Figure 3: Female breast cancer incidence and mortality rates by race and ethnicity, US, 2006-2010[26,29,30]

The association between HER2 overexpression and tumor pathogenesis in BC, together with the accessibility of the extracellular domain of the receptor, has made HER2 a suitable target for antibody therapy.[29,31-33]

Previously three drugs, namely, trastuzumab (in 1998), lapatinib (in 2007), and pertuzumab (in 2012) have been approved by Food and Drug Administration (FDA) to treat HER2-positive BC.[34] Trastuzumab [Figure 4a] a humanized anti-HER2 monoclonal antibody and lapatinib [Figure 4b] is a twin RTK inhibitor that reduces both HER1 and HER2.[35,36] pertuzumab (humanized monoclonal antibody) binds to the extracellular domain of HER2.[37]

ADO-TRASTUZUMAB EMTANSINE (T-DM1) AN FDA APPROVED DRUG

TDM1 is a new (fourth) approved drug, and it is used for the treatment of HER2-positive mBC in patients who have been treated previously with trastuzumab and a taxane, and who have already been treated for mBC or developed tumor recurrence within 6 months of adjuvant therapy. It is marketed in many countries such as Europe, Canada, US, Switzerland, and Japan. T-DM1 has been approved by U.S. FDA in February 2013.[38-40] T-DM1 received European Commission approval on November 2013 based on results from the pivotal Phase III EMILIA trial and Switzerland is the first country which has the marketing permission for T-DM1 in Europe.[5] In September 2013, it received marketing approval in Japan based on results from a Japanese Phase II trial and the EMILIA Phase III trial and also approved by the Health Canada.[41]

T-DM1 is also known as TDM1, and the trade name is kadcyla. TDM1 is an antibody-drug conjugate (ADC) and a highly complex prodrug. ADC is composed of an antibody trastuzumab (humanized anti-HER2 IgG1), a stable, non-reducible linker mitotic checkpoint complex (MCC) (N-Succinimidyl-(maleimidomethyl) cyclohexane) and tubulin polymerization inhibitors (DM1). The source of ADC can be outlined reverse over a century to the Paul Ehrlich (German physician and scientist), who suggested the theory of selectively distributing a cytotoxic medicine to a tumor through a targeting agent (ADC). DM1 is obtained from the extremely effective antitumor agent maytansine.

Trastuzumab is a recombinant monoclonal antibody produced by mammalian (Chinese hamster ovary) cells. The small molecular components (DM1 and MCC) are produced by chemical synthesis. Trastuzumab [Figure 5] alone stops the growth of cells by binding to the HER2/neu receptor. TDM1 contains an average of 3.5 DM1 molecules per antibody.[42-44] Features and properties of this are shown in Table 2.

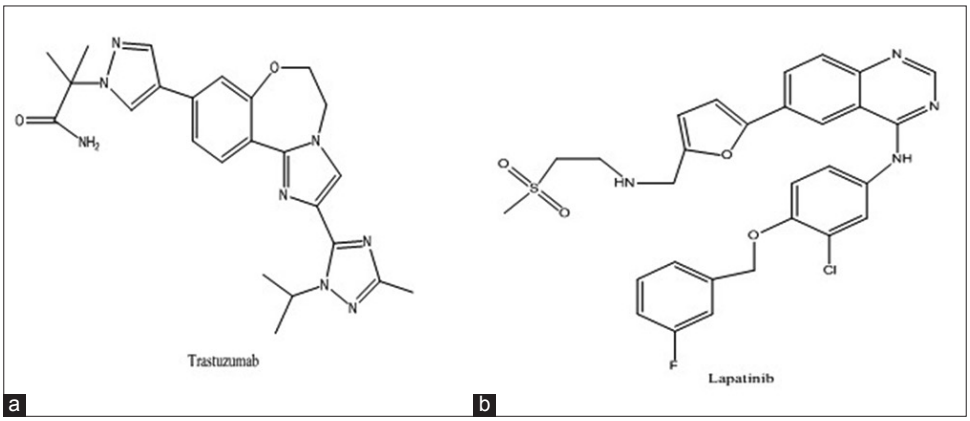

Figure 4: Structure of, (a) Trastuzumab, (b) Lapatinib

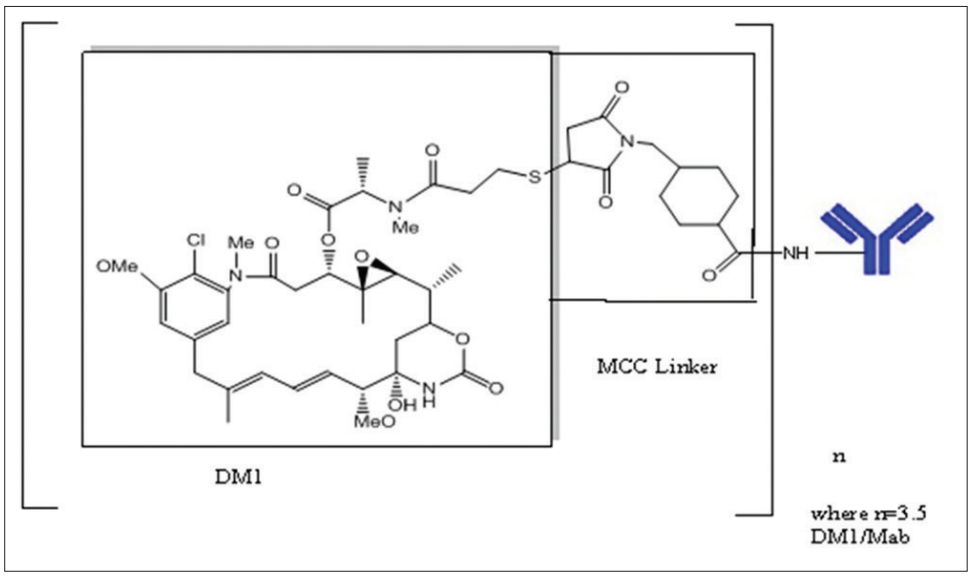

Figure 5: Chemical structure of ado-trastuzumab emtansine

PHARMACODYNAMIC AND MECHANISM OF ACTION

TDM1 is an ADC.[17] ADC consist of monoclonal antibody trastuzumab which covalently linked with DM1 (cytotoxin, microtubule inhibitor) by the MCC linker (Stable, non-reducible).[45,46] On binding to HER2, The HER2–T-DM1 complex is endocytosed by receptor-mediated process and ultimately fused with a lysosome where it undergoes proteolytic degradation with the release of the active DM1, the trastuzumab component and exerts its antitumor effects [Figure 6]. The primary active metabolite, lysine–SMCC–DM1, does not readily cross the plasma membrane and therefore does not cause any effect in neighboring cells but it mitotically disrupts the microtubule network of HER2-overexpressing cell by binding to tubulin which ultimately leads to cell cycle arrest at G2-M phase and causes apoptotic cell death.[11] Figure 7 shows the apoptosis of the cells, as well as the presence of cells with aberrant mitotic figures and a giant multinucleated structure, indicates the mitotic catastrophy of HER2-overexpressing cell after prolonged xenografting with T-DM.[47-49]

PHARMACOKINETICS

The pharmacokinetics of T-DM1 were evaluated in the phase 1 study along with the pharmacokinetic analysis of T-DM1 conjugate (ADC) which is done using pooled data from trials of patients having BC. The data obtained is then analyzed in a linear two-compartment model along with first-order elimination from the central compartment which

Table 2: Some important properties of ado-trastuzumab emtansine

Synonyms	**T-DM1, trastuzumab-DM1, trastuzumab-MCC-DM1 antibody-drug conjugate**
Category	Anticancer (metastatic breast cancer)
Manufacturer	Genentech
Original source	*Maytenus serrata* (plant)
Mechanism of action	Tubulin depolarization
Drug release mechanism	Peptidase and linker degradation
Free drug potency (EC50)	10–11–10–12 M
Ab-drug linker	Peptide-thioether through cysteine residues on mAb
Drug-mAb ratio	Less homogeneous□3.5
Route of administration	Intravenous infusion
Dose	3.6 mg/kg every 3 weeks
Pharmacokinetics	Bound to plasma protein, metabolized by CYP3A4/5, clearance level 0.68 L/day, $t_{1/2}$ 4 days
Adverse reaction	Hepatotoxicity, left ventricular dysfunction, embryo-fetal toxicity, pulmonary toxicity, thrombocytopenia, peripheral neuropathy
Shelf life	3 Years
ATC code	L01XC14
Chemical formula	$C_{6448}H_{9948}N_{1720}O_{2012}S_{44.}$ $(C_{47}H_{62}ClN_4O_{13}S)_n$
Molecular weight	148.5 kDa

T-DM1: Ado-trastuzumab emtansine, MCC: Mitotic checkpoint complex

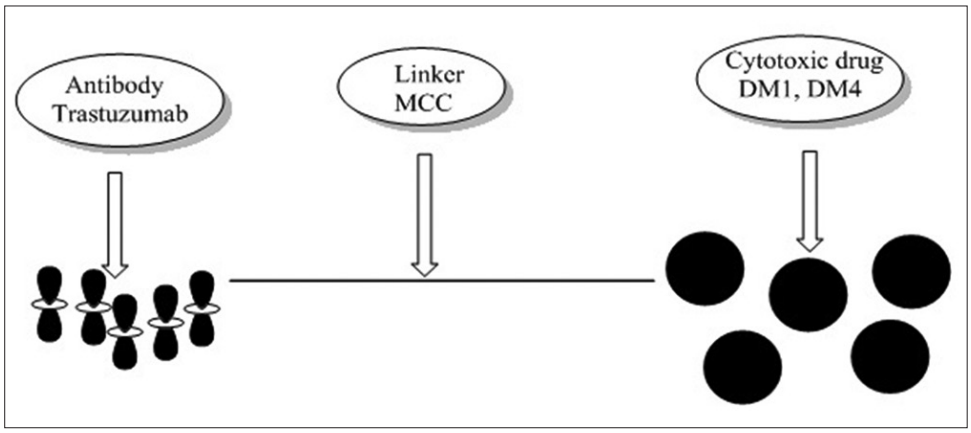

Figure 6: Schematic diagram of antibody-drug conjugate

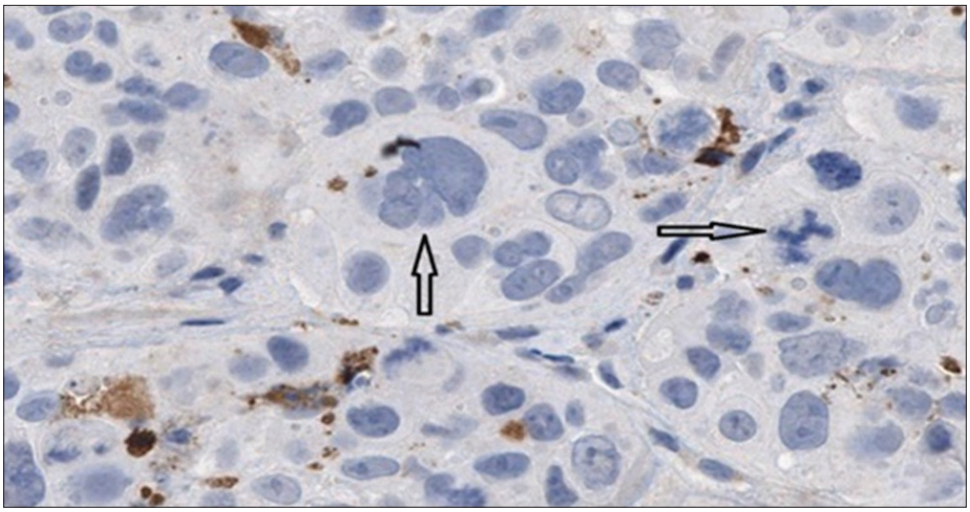

Figure 7: Histological findings in a human epidermal growth factor receptor-2-positive, trastuzumab, and lapatinib-resistant breast cancer (JIMT-1) xenograft following trastuzumab emtansine treatment. Numerous apoptotic cells are present (stained brown with CytoDeath staining). Hematoxylin counterstain reveals multinucleated giant cells and pathological mitoses (arrows), which are hallmarks of mitotic catastrophe[50]

in turn depicts the ADC concentration-time profile. The pharmacokinetics of T-DM1 are as follows.

Absorption

Trastuzumab emtansine is only administered through intravenous route. There have been no other studies reported with other routes. The maximum plasma concentration (C_{max}) of Trastuzumab emtansine is 74.3 ± 20.1 mcg/kg and the systemic exposure (AUC) is 295.2 ± 65.4 mcg•d/mL when the patients received doses of 3.6 mg/kg every 3 weeks. The terminal half-life ($T_{1/2}$) of Trastuzumab emtansine is found to be 3.5 ± 0.8 days, and the volume of distribution (V_d) is 60 ± 13.6 mL/kg.[51] The maximum plasma concentration (C_{max}) of Trastuzumab emtansine is 54.8 ± 12.6 mcg/kg, $T_{1/2}$ is 3.4 ± 1.1 days, AUC is 198.5 ± 54.5 mcg d/mL, and the Vd is 55.4 ± 13 mL/kg.6 when the patients received doses of 2.4 mg/kg weekly.[52]

Distribution

In the distribution study, the maximum concentration (C_{max}) of ADC and MC1 were found at the end of the infusion. In the phase-I study, the mean standard deviation of ADC and DM1 followed by T-DM1 administration was found to be 83.4 µg/mL and 4.61 ng/mL, respectively.

In the *in-vitro*, analysis the plasma protein binding of DM1 was found to be 93%, and it was also found that DM1 was a substrate of p-glycoprotein. Based on the population pharmacokinetics study, the central volume of distribution of ADC was found to be 3.13 L.[38-40,44]

Metabolism

In the *in-vitro* study, it was observed that MD1 and a small molecule component of Kadcyla were metabolized by CYP3A4/5. It was also observed that MD1 is not inhibited or induced by major CYP450 enzymes. Catabolites of T-DM1 such as the MCC- DM1, Lys-MCC-DM1, and DM1 was found to at a very low level in the human plasma.[38-40,44]

Elimination

Based on the pharmacokinetic study, followed by the intravenous infusion of Kadcyla, it is observed that the clearance level of ADC was 0.68 L/day and an elimination half-life ($t_{1/2}$) of approximately 4 days. It was also observed that no accumulation was seen even after a repetitive intravenous infusion of KADCYLA for 3 weeks.

Based on the pharmacokinetics study of patients having a renal impairment which include moderate (CL_{cr} 30-59 mL/min) and mild (CL_{cr} 60-89 mL/min) renal impairment, depicts that the ADC is not affected renal impairment as compared to the normal renal function ($CL_{cr} \geq 90$ mL/min).[38-40,44]

CLINICAL TRIALS

Patients (991) were randomly assigned in a 1:1 ratio to kadcyla or lapatinib plus capecitabine. Patients in the trial [Figure 8] must have received therapy with a taxane and trastuzumab before enrollment.[44] A randomized, multicenter, openlable trial compared kadcyla 3.6 mg/kg intravenously on day 1 of a 21-day cycle (n = 495) and lapatinib at 1250 mg/day orally once per day of a 21-day cycle plus capecitabine at 1000 mg/m^2 orally twice daily on days 1-14 of a 21-day cycle (n = 496) in patients with previously treated mBC.[47] At the time of the primary analysis, median time on study drug was 5.7 months (range: 0-28.4) for kadcyla, 4.9 months (range: 0-30.8) for lapatinib, and 4.8 months (range: 0-30.4) for capecitabine. The

progression-free survival (PFS) of kadcyla or lapatinib plus capecitabine was 9.6 months and 30.9 months. The overall survival (OS) of kadcyla or lapatinib plus capecitabine were 6.4 months and 25.1 months.[53-55]

On July 25, 2013, genentech/roche announced that a Phase 3 trial comparing Kadcyla to the physician's choice of treatment in patients with HER2-positive BC who have already been treated with an HER2-targeted therapy, met its coprimary endpoint of progression-free survival. The other endpoint is OS [Figures 9 and 10], but these data are not yet mature.[56]

DRUG-DRUG INTERACTIONS

Microtubule inhibitor DM1 (also known as cytotoxic component) of ADC is metabolized mainly by an enzyme CYP3A4. However, CYP3A5 enzyme is less responsible for the metabolism of DM1. It should be also kept in mind that continuous use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) with kadcyla should be avoided because it causes a potential rise in DM1exposure and toxicity. To solve this problem, kadcyla treatment is being delayed until the stronger CYP3A4 inhibitors have cleared from circulation.[39,40,44]

ADVERSE REACTION

Hepatotoxicity

In clinical trials of kadcyla, severe hepatotoxicity, including drug-induced liver injury and hepatic encephalopathy was reported. Nodular regenerative hyperplasia of the liver has been also identified from liver biopsies. In trial condition, the concentration of serum transaminase is increased. Before the treatment, serum transaminases and bilirubin should be controlled.

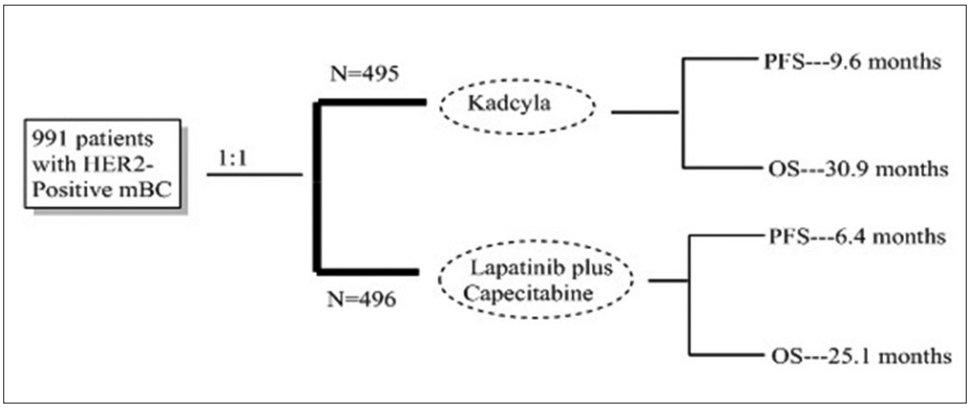

Figure 8: Trials profile of ado-trastuzumab emtansine (Kadcyla)

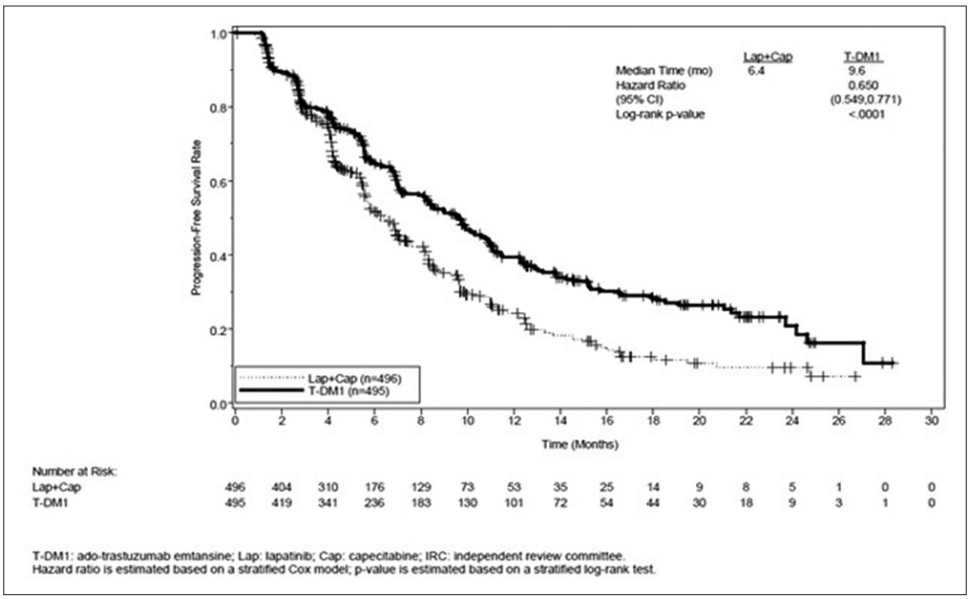

Figure 9: Kaplan-Meier curve of IRC-assessed progression-free survival for study 1[44]

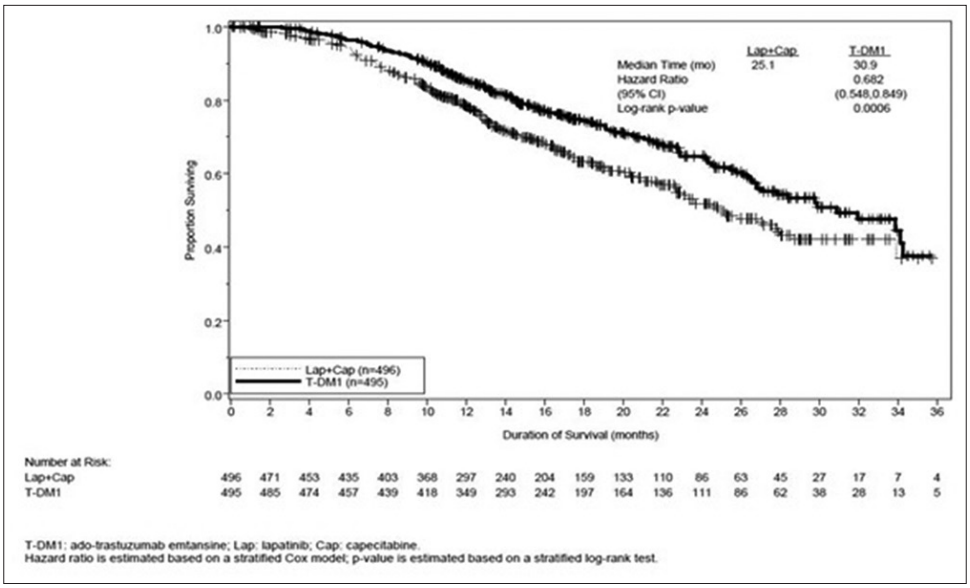

Figure 10: Kaplan-Meier curve of overall survival for study 1[44]

Left ventricular dysfunction

In study 1, the percentage of adverse reaction of the left ventricular dysfunction of kadcyla treated group is 1.8%, and lapatinib plus capecitabine-treated group is 3.3%.

Embryo-fetal toxicity

When T-DM1 is administered with monoclonal antibody in case of pregnancy, it causes various adverse reactions such as oligohydramnios, fetal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on the mechanism of action, the microtubule inhibitor DM1 (cytotoxin) in ADC sometimes cause embryo-fetal toxicity.

Pulmonary toxicity

In clinical trials with kadcyla, it has been found various pulmonary toxicity such as pneumonitis, interstitial lung disease, acute respiratory distress syndrome, or fetal outcome.

Hypersensitivity reactions, infusion-related reactions

In clinical trials of kadcyla, various infusion-related reactions are found. These are:

- Tachycardia
- Bronchospasm
- Wheezing
- Hypotension
- Dyspnea
- Pyrexia
- Chills
- Flushing.

Hypersensitivity reactions such as allergic/anaphylactic-like reaction have been observed in clinical trials of single-agent kadcyla.

Thrombocytopenia

In study 1, the percentage of adverse reaction of thrombocytopenia of kadcyla-treated group is 31.2%, and lapatinib plus capecitabine-treated group is 3.3%. Before the treatment, platelet counts should be monitored.

Neurotoxicity

Peripheral neuropathy was reported in clinical trials of kadcyla. In study 1, the percentage of the adverse reaction of peripheral neuropathy of kadcyla-treated group is 21.2%, and lapatinib plus capecitabine-treated group is 13.5%.

Others

The other most common adverse reactions are:

- Nausea
- Fatigue
- Pain in the muscles or joints
- Increased liver enzymes
- Headache and
- Constipation.[44]

Miscellaneous information

Ingredients

The active ingredient of kadcyla includes trastuzumab emtansine. Inactive ingredients include succinic acid, sodium hydroxide, sucrose, and polysorbate 20.

Dosage and administration

The recommended dose is 3.6 mg/kg in every 3 weeks (21 days cycle). The dose should be maintained till it reaches maximum therapeutic level. It should also be kept in mind that kadcyla should not be administered at a dose greater than 3.6 mg/kg. It is administered through intravenous infusion and should not be submitted with trastuzumab.[45,57]

Cost

According to the opinion of Genentech, the cost of kadcyla is about $9,800 for a month and $94,000 for a typical course of treatment. This is about twice the price of Herceptin.[39]

Storage and supplied

T-DM1 should not be frozen or shake. It is stored in vials in a refrigerator at 2°C-8°C (36°F-46°F). It is supplied in a single-use vial (100 mg vial) or single-use vial (160 mg vial).[39,44]

Treatment of special populations with special care

Pregnancy

Kadcyla should not be administered to a pregnant woman because it causes a potential hazard to the fetus. TDM1 is an ADC. ADC consists of two components such as trastuzumab and DM1. They cause fetal harm or death when administered to a pregnant woman. It should be reported to the Genentech adverse event line at 1-888-835-2555 if kadcyla is administered during pregnancy.

Nursing mothers

IgG is secreted in human milk, but it has not a clear idea about kadcyla whether it also secreted or not. It has been reported that trastuzumab is secreted in small amounts in breast milk and causes various adverse reactions to nursing mothers as well as the neonate. To prevent adverse reaction, it should be kept in mind that the mother should not be treated with kadcyla or should be discontinued from the treatment.

Females of reproductive potential

Females should be advised to use contraceptives while receiving kadcyla as it may cause an adverse reaction to embryo-fetal.

Renal and hepatic impairment

No dose adjustment was recommended for patients with severe renal and hepatic impairment.[39,40,44]

Brands for mBC

The following list [Table 3] describes an update on information about the various products use for the treatment of mBC.[58]

CONCLUSION

Nowadays, BC is the most common cancer in the United States and other parts of the globe. Hence, the treatment of BC is essential for a healthy lifestyle. T-DM1 (T-DM1, kadcyla) is a new drug which got the approval on 22 February 2013 from US-FDA for marketing. The trials conducted so far have proven to be worth in treating HER2+ metastatic disease. The trials are going on to address its role in front-line metastatic and nonmetastatic diseases. T-DM1 is a single-agent (3.6 mg/kg), and it is predictable, well characterized,

Table 3: Different brands used for mBC

Product Name	Licensee	Approve indications
Avastin	Genentech (US) and Roche (ex-US)	Metastatic colorectal cancer Advanced non-small cell lung cancer Renal cancer Metastatic HER2 - breast cancer Glioblastoma Ovarian cancer
Herceptin	Genentech (US) and Roche (ex-US)	Metastatic HER2+breast cancer Metastatic HER2+stomach cancer
Lucentis	Genentech (US) and Novartis (ex-US)	Wet AMD Macular edema or swelling following retinal vein occlusion Diabetic macular edema
Actemra	Roche and Chugai	Moderate to severe RA, including patients who have had an inadequate response to one or more DMARDS
Kadcyla	Genentech (US) and Roche (ex-US)	Second line metastatic HER2+breast cancer First line in patients with metastatic HER2+breast cancer with disease recurrence within 6 months of adjuvant treatment

HER2: Human epidermal growth factor receptor, mBC: Metastatic breast cancer, RA: Rheumatoid arthritis, AMD: Age-related macular degeneration

and unaffected by circulating levels of HER2 extracellular domain or residual trastuzumab but being a highly therapeutic molecule, acquired resistance to T-DM1 has been observed. This article highlights about description about kadcyla for the treatment of patients with HER2-positive mBC.

REFERENCES

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43-66.
2. Health Canada approves KADCYLA™ (trastuzumab emtansine) for the treatment of HER2-positive metastatic breast cancer. Available from: http://www.newswire.ca/en/story/1223743/health-canada-approves-kadcylatm-trastuzumab-emtansine-for-the-treatment-of-her2-positive-metastatic-breast-cancer. [Last accessed on 2016 Aug 15].
3. Ghumare SS, Cunningham JE. Breast cancer trends in Indian residents and emigrants portend an emerging epidemic for India. Asian Pac J Cancer Prev 2007;8:507-12.
4. Badwe RA, Gupta S. Breast cancer: An Indian perspective. National Med J India 2011;24:193-7.
5. Roche's Kadcyla approved in the EU for advanced HER2-positive breast cancer. Media Release. Available from: http://www.roche.com/media/media_releases/med-cor-2013-11-20.html. [Last accessed on 2016 Aug 15].
6. Olson JS. Bathsheba's Breast: Women, Cancer and History. 1st ed. Baltimore: The Johns Hopkins University Press; 2005. p. 199-200.
7. Kumar A, Hegde RR, Lohani A, Verma A. First global approval of eribulin mesylate for treatment of metastatic breast cancer. J Fundam Pharm Res 2014;2:7-21.
8. Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, *et al*, editors. SEER Cancer Statistics Review, 1975-2010. Bethesda, MD: National Cancer Institute; 2013. Available from: http://www.seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER Data Submission. [Last accessed on 2015 Mar 15].
9. Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN. Breast carcinoma in men: A population-based study.Cancer 2004;101(1):51-7.
10. 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;279:922-9.
11. Schwartz GF, Hughes KS, Lynch HT, Fabian CJ, Fentiman IS, Robson ME, *et al*. Proceedings of the international consensus Conference on breast cancer risk, genetics, and risk management, April, 2007. Cancer 2008;113:2627-37.
12. Turnbull C, Rahman N. Genetic predisposition to breast cancer: Past, present, and future. Annu Rev Genomics Hum Genet 2008;9:321-45.
13. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007;25:1329-33.
14. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, *et al*. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: A combined analysis of 22 studies. Am J Hum Genet 2003;72:1117-30.
15. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Alcohol consumption and ethyl carbamate. IARC Monogr Eval Carcinog Risks Hum 2010;96:1383.
16. Chen WY, Rosner B, Hankinson SE, Colditz GA,Willett WC. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. JAMA 2011;306:1884-90.
17. Allen NE, Beral V, Casabonne D, Kan SW, Reeves GK, Brown A. Moderate alcohol intake and cancer incidence in women. J Natl Cancer Inst 2009;101:296-305.
18. Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW Jr, *et al*. Alcohol, tobacco and breast cancer-collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer 2002;87:1234-45.
19. Suzuki R, Orsini N, Mignone L, Saji S, Wolk A. Alcohol intake and risk of breast cancer defined by estrogen and progesterone receptor status-a meta-analysis of epidemiological studies. Int J Cancer 2008;122:1832-41.
20. Singletary KW, Gapstur SM. Alcohol and breast cancer: Review of epidemiologic and experimental evidence and potential mechanisms. JAMA 2001;286:214321-51.
21. Li CI, Chlebowski RT, Freiberg M, Karen CJ, Lewis K, Dorothy L, *et al*. Alcohol consumption and risk of postmenopausal breast cancer by subtype: The women's health initiative observational study. J Natl Cancer Inst 2010;102:1422-31.
22. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. New Engl J Med 2006;354:270-82.
23. La VC, Giordano SH, Hortobagyi GN, Chabner B. Overweight, obesity, diabetes, and risk of breast cancer: Interlocking pieces of the puzzle. Oncologist 2011;6:726-9.
24. Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, O'Meara ES, *et al*. Risk factors for breast cancer for women aged 40 to 49 years: A systematic review and meta-analysis, Ann Intern Med 2012;156:635-48.
25. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN. Proportion of breast cancer cases in the United States explained by well-established risk factors. J Natl Cancer Inst 1995;87:1681-5.
26. DeSantis C, Siegel R, Ahmedin J. Breast Cancer Facts & Figures 2011-2012. Atlanta, GA: American Cancer Society Inc.; 2012.
27. Alteri R. Breast cancer Facts and Figures 2011-2012. Atlanta, GA: American Cancer Society Inc., Corporate Center; 2012.

28. Gaudet MM, Gapstur SM, Sun J, Diver WR. Active smoking and breast cancer risk: Original cohort data and meta-analysis. J Natl Cancer Inst 2013;105:515-25.
29. Schlessinger J. Ligand-induced, receptor-mediated dimerization and activation of EGF receptor. Cell 2002;110:669-72.
30. Incidence - North American Association of Central Cancer Registries, 2013. US Mortality Data - National Center for Health Statistics, Centers for Disease Control and Prevention. American Cancer Society, Surveillance Research, 2014. Available from: http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-041785.pdf. [Last accessed on 2016 Aug 15].
31. Copeland G, Lake A, Firth R. Cancer in North America: 2006-2010. Combined Cancer Incidence for the United States, Canada and North America. Vol. 1. Springfield, IL: North American Association of Central Cancer Registries Inc.; 2013.
32. Teicher BA, Doroshow JH. The promise of antibody-drug conjugates. N Engl J Med 2012;367:1847-8.
33. Poon KA, Flagella K, Beyer J, Tibbitts J, Girish S, Dybdal N, *et al*. Preclinical safety profile of trastuzumab emtansine(T-DM1): Mechanism of action of its cytotoxic component retained with improved tolerability. Toxicol Appl Pharmacol 2013;273:298-313.
34. Rastogi V, Yadav P, Bhattacharya SS, Mishra AK, Verma A, Pandit JK. Carbon Nanotubes: An emerging drug carrier for targeting cancer cells. J Drug Del 2014: 2014:670815.
35. FDA approves Kadcyla (ado-trastuzumab emtansine), a new therapy for patients with HER2-positive, late-stage (metastatic) breast cancer. Available from: https://newdrugapprovals.org/2013/02/23/fda-approves-kadcyla-ado-trastuzumab-emtansine-a-new-therapy-for-patients-with-her2-positive-late-stage-metastatic-breast-cancer. [Last accessed on 2016 Aug 15].
36. Vu T, Claret FX. Trastuzumab: Updated mechanisms of action and resistance in breast cancer. Front oncol 2012;2:1-6.
37. Medina PJ, Goodin S. Lapatinib: A dual inhibitor of human epidermal growth factor receptor tyrosine kinases. Clin Thera 2008;30:1426-46.
38. Capelan M, Pugliano L, Azambuja ED, Bozovic I. Pertuzumab: New hope for patients with HER2-positive breast cancer. Anna Oncol 2012;24(2):1-10.
39. Roche HL. New data from Phase III EMILIA study showed Roche's trastuzumab emtansine (T-DM1) significantly improved survival of people with HER2-positive metastatic breast cancer (Press release), 2012-08-27. Available from: http://www.roche.com/media/store/releases/med-cor-2012-08-27.htm. [Last retrieved on 2013 Feb 23].
40. Pollack AF. Approves a new drug for advanced breast cancer. The New York Times. http://www.nytimes.com/2013/02/23/business/fda-approves-breast-cancer-drug.html?_r=0 [Last retrieved 2013 Feb 22].
41. FDA approves new treatment for late stage breast cancer (Press release). U.S. Food and Drug Administration. 2013-02-22. Available from: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm340704.htm. [Last retrieved 2013 Feb 22].
42. Roche Launches Kadcyla in Japan. Available from: http://www.news.yahoo.com/roche-launches-kadcyla-japan-220012362.html. [Last accessed on 2015 May 06].
43. Girish S, Gupta M, Wang B, Lu D, Krop IE, Vogel CL, *et al*. Clinical pharmacology of trastuzumab emtansine (T-DM1): An antibody-drug conjugates in development for the treatment of HER2-positive cancer. Cancer Chemother Pharmacol 2012;69:1229-40.
44. Lewis Phillips GD, Li G, Dugger DL, Crocker LM, Parsons KL, Mai E, Blättler WA, *et al*. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res 2008;68:9280-90.
45. Food and Drug Administration. Kadcyla package insert: Prescribing information. Kadcyla (ado-trastuzumab emtansine) lable- Accessdata FDA. Available from: http://www. accessdata. Fda. Gov/drugsatfda_docs/label/2013/125427IbI pdf. [Last accessed on 2014 Jun 10].
46. LoRusso PM, Weiss D, Guardino E, Girish S. Trastuzumab emtansine: A unique antibody-drug conjugates in development for human epidermal growth factor receptor 2-positive cancer. Clin Cancer Res 2011;17:6437-47.
47. FDA denies accelerated approval of Genentech's trastuzumab-DM1 (T-DM1) BLA for metastatic breast cancer (Press release). Genentech. 2010-08-27. Available from: https://www.gene.com/media/press-releases/12947/2010-08-26/genentech-provides-update-on-fda-applica. [Last retrieved on 2013 Feb 23].
48. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, *et al*. Trastuzumab emtansine for HER2-positive advanced breast cancer.N Engl J Med 2012;367:1783-91.
49. Peddi PF, Hurvitz SA. Trastuzumab emtansine: The first targeted chemotherapy for treatment of breast cancer. Future Oncology 2013;9:319-26.
50. Barok M, Joensuu H, Isola J. Trastuzumab emtansine: Mechanisms of action and drug resistance. Breast Cancer Res 2014;16:209.
51. Barok M, Tanner M, Koninki K, Isola J. Trastuzumab-DM1 causes tumour growth inhibition by mitotic catastrophe in trastuzumab-resistant breast cancer cells *in vivo*. Breast Cancer Res 2011;13:R46.
52. Krop IE, Beeram M, Modi S, Jones SF, Holden SN, Yu W, *et al*. Phase I study of trastuzumab-DM1, an HER2 antibody-drug conjugate, given every 3 weeks to patients with HER2-positive metastatic breast cancer. J Clin Oncol 2010;28:2698-704.
53. Beeram M, Krop IE, Burris HA, Girish SR, Yu W, Lu MW, *et al*. A phase 1 study of weekly dosing of trastuzumab emtansine (T-DM1) in patients with advanced human epidermal growth factor 2-positive breast cancer. Cancer 2012;118:5733-40.

54. ClinicalTrials. Gov NCT01120184 A Study of Trastuzumab Emtansine (T-DM1) Plus Pertuzumab/ Pertuzumab Placebo versus Trastuzumab (Herceptin) Plus a Taxane in Patients With Metastatic Breast Cancer (MARIANNE). Available from: https://www.clinicaltrials.gov/ct2/show/NCT01120184. [Last retrieved on 2013 Feb 23].
55. ClinicalTrials. Gov NCT01419197 A Study of Trastuzumab Emtansine in Comparison With Treatment of Physician's Choice in Patients with HER2-Positive Breast Cancer Who Have Received at Least Two Prior Regimens of HER2-Directed Therapy (TH3RESA). Available from: https://www.clinicaltrials.gov/ct2/show/NCT01419197. [Last retrieved on 2013 Feb 23].
56. ClinicalTrials. Gov NCT01641939 A Study of Trastuzumab Emtansine Versus Taxane in Patients with Advanced Gastric Cancer. Available from: http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/adopted-names.page. [Last retrieved on 2013 Feb 23].
57. RBC Capital Markets. Global Healthcare Conference; 2014. Available from: http://www.pdl.com/wp-content/uploads/2010/07/2014-RBC-Capital-Markets-Global-Healthcare-Conference.pdf. [Last accessed on 2016 Aug 15].
58. USAN Council. Statement on a Nonproprietary Name Adopted by the Usan Council: Trastuzumab Emtansine. American Medical Association; 2009. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01641939. [Last retrieved on 2013 Feb 22].

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