Journal of Applied Pharmaceutical Research
Volume 12 Issue 2, Year of Publication 2024, Page 35 – 41
DOI: 10.18231/j.joapr.2024.12.2.35.41

Check for updates

Research Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | ***JOAPR***
www.japtronline.com ***ISSN: 2348 – 0335***

A SINGLE CENTRE, REAL WORLD EXPERIENCE OF T-DM1 IN THE TREATMENT OF HER2-POSITIVE METASTATIC BREAST CANCER PATIENTS IN INDIA

Vindhya Vasini Andra[1]*, Mohana Vamsy[2], Monal Dayal[3], Pawan Shinkar[4]

Article Information
Received: 19th January 2024
Revised: 3rd April 2024
Accepted: 11th April 2024
Published: 30th April 2024

Keywords
Real world evidence, HER2 positive, metastatic breast cancer, T-DM1, Biosimilar

ABSTRACT

Background: HER2 (Human Epidermal Growth Receptor 2) positive breast cancer is an aggressive subtype. Treatment for patients with HER2-positive breast cancer has advanced significantly over time with the introduction of targeted therapies like trastuzumab, pertuzumab, lapatinib, trastuzumab emtansine, trastuzumab, deruxtecan, and tucatinib. In a lower-middle-income nation, accessibility is still problematic for any newer therapy. This study aimed to describe the safety and practical effectiveness of the first T-DM1 biosimilar in India for treating patients with HER2-positive mBC. **Methodology:** This is a retrospective, observational, single-center study of patients with HER2-positive metastatic breast cancer treated with T-DM1 biosimilar. The study involved 16 mBC patients. The primary goal was to assess T-DM1's effectiveness regarding PFS and ORR, with safety and OS as the secondary goals. **Results:** The ORR was observed to be 81.3%. One (6.29%) of the patients achieved CR, while 3 patients (18.8%) are on stable disease, and 12 patients (75 %) achieved PR. The major adverse events reported among study patients were thrombocytopenia (31.25%) and anemia (31.25%), followed by neutropenia, hyperglycemia, and fatigue in 12.5 % of cases. Grade 3 thrombocytopenia was seen in 2 patients, and grade 3-4 fatigue was observed in 1 patient. Median PFS was nearly six months, and OS data is available for only 25% of patients; the rest continue the therapy. **Conclusion:** This retrospective observational study offers significant information about the safety and efficacy of T-DM1 biosimilar in treating HER2-positive mBC.

INTRODUCTION

HER2 (Human Epidermal Growth Receptor 2) positive breast cancer is an aggressive subtype that is characterized by abnormal amplification of HER2 proteins, resulting in uncontrolled cell growth and proliferation [1,2]. About 2.3 million cases of breast cancer are reported every year globally. However, around 80%

[1]*Department of Medical Oncology, Omega Hospitals, Hyderabad, Telangana 500034, India*
[2]*Department of Surgical Oncology, Omega Hospitals, Hyderabad, Telangana 500034, India*
[3]*Department of Pathology, Omega Hospitals, Hyderabad, Telangana 500034, India*
[4]*Department of Radiology, Omega Hospitals, Hyderabad, Telangana 500034, India*

For Correspondence: **drvindhya@gmail.com**

of deaths from breast cancer occur in low- and middle-income countries [3]. In India, between 20 and 50 percent of all cases of breast cancer are HER2-positive, and the number of cases is steadily rising in both rural and urban areas [3]. According to epidemiological research, 50% of Indian women receive a stage III or IV diagnosis of HER2-positive breast cancer [4].

HER2 is an orphan membrane receptor that causes dysfunction of pathways, such as the Phosphoinositide-3-kinase [PI3K]/Akt signaling pathway and protein kinase C [PKC] activation pathway, which works as an oncogenic driver in breast cancer [4,5]. HER2 proto-oncogene shows abnormal growth and excessive expression of malignant cells and harms survival rates as compared to other breast cancer subtypes [6]. Due to poor prognosis and high relapse rate, early detection and prompt treatment should be the approach for this subtype, as inadequate treatment leads to highly rapid and aggressive tumor growth [7]. Depending on the stage, kind, and features of the tumor, there are various therapeutic options for HER2-positive breast cancer, including surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy. The monoclonal antibody trastuzumab is combined with the strong microtubule-disrupting agent maytansinoid, DM1, to form trastuzumab emtansine (T-DM1). T-DM1 is joined by a stable linker, which results in cytotoxic effects when released in the cancer cell. It selectively binds to HER2 proto-oncogene to induce apoptosis and cell immunity, while emtansine inhibits tubulin polymerization, which in turn prohibits the HER2 signaling, causing cell-cycle arrest[4,8].

T-DM1 specifically targets the HER2 over-expressing cancer cells, further reducing systemic adverse events. It is considered the standard of care in patients who received prior trastuzumab and taxane. The high cost of T-DM1 poses a significant barrier to accessibility for many patients. Thus, owing to the therapeutic advantages of T-DM1, its biosimilar (ZRC-3256), after proving its similarity in terms of efficacy and safety, got approved and is made available in India with better accessibility for the benefit of patients [9–11]. In this retrospective study, we report our first experience with T-DM1 biosimilars in our routine clinical practice. By evaluating the objective response rates [ORR], progression-free survival [PFS], overall survival [OS], and adverse events in patients with metastatic HER2-positive breast cancer in this Indian patient cohort, we aim to evaluate the effectiveness and safety of this medication.

METHODOLOGY

Study Design and Patients

This study analyzed data from patients with metastatic HER2-positive breast cancer that was conducted retrospectively and observationally at a single-site tertiary care center between June 2021 and December 2022. The institutional ethics committee approved using the existing patient data for this retrospective study and generating the T-DM1 biosimilar (UJVIRATM) data for Indian patients. The hospital system reviewed the medical records of each patient to retrieve the information needed regarding patient characteristics, previous treatment, and pathological characteristics. A total of 16 HER2 positive (defined as IHC 3+ or 2+ with FISH positive) breast cancer patients data, aged 18 years or older, were eligible to be included in the study. Before receiving T-DM1, the Eastern Cooperative Oncology Group (ECOG) performance status was verified as a score of 2 or lower. The study included patients treated with T-DM1 for metastatic HER2-positive breast cancer, irrespective of the presence of concomitant comorbidities. Demographic details of these patients along with the stage of diagnosis, details of adjuvant treatment, and any previous treatment(s) for the metastatic disease before T-DM1, line of T-DM1 administration, adverse effects of T-DM1 and reasons for further treatment alteration were taken into consideration. The records of the dates of starting the T-DM1 therapy and the discontinuation of the therapy in patients were also recorded. The details were collected in a structured and approved electronic case record form developed for the study.

Outcome

The primary outcome consisted of an evaluation of PFS and ORR. The secondary outcome was to evaluate the safety and OS of the patients. Echocardiography was performed at baseline before initiating T-DM1 therapy and every three months. The evaluation of brain metastases was performed using contrast-enhanced MRI or CT. Radiologists assessed the existence of metastases and tumor response to T-DM1 therapy. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, version 4.0.

Statistical Analysis

Descriptive analysis was performed on the data. A version of IBM SPSS 21.0 was used to generate Kaplan Meier Curves. The Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 defined the ORR as complete and partial response

(CR+PR). PFS is the time between the disease's progression or death and the first T-DM1 dose. Since Kaplan Meier analysis offers a comprehensive picture of data, including the beginning of treatment and disease progression or relapse, it was used to measure the PFS. OS was defined as the amount of time that passed between the first T-DM1 dosage and death. P-values less than 0.05 were deemed statistically significant.

Table 1. Baseline characteristics of study patients

Age -Years Median (Range)	53.5 (36-71)	
Weight – Kg Median (Range)	68 (44-101)	
Other Comorbidities	**N**	**%**
Hypertension	4	25.0
Diabetes Mellitus	4	25.0
ECOG Score		
0	3	18.8
1	12	75.0
2	1	6.3
Hormone receptor status		
ER and/or PR+/HER2+	12	75
ER− and PR−/HER2+	4	25
Visceral Involvement		
No	7	43.8
Yes	9	56.2
Brain Involvement		
No	10	62.5
Yes	6	37.5
Number of metastatic sites		
<2	6	37.5
≥2	10	62.5
Stage of initial diagnosis		
2	2	12.5
3	8	50.0
4	6	37.5
Disease status at current presentation		
De novo metastatic	6	37.5
EBC/LABC prior, now progressed to MBC	10	62.5

Abbreviation: EBC, Early Breast Cancer; MBC, Metastatic breast cancer, LABC, Locally advanced breast cancer;

RESULTS

Patient's characteristics

All the patients who were administered with T-DM1 were in a metastatic disease. The median age of the patients was 53.5 years. The collected data also showed that nearly 25% of patients presented with different comorbidities, such as Diabetes Mellitus and Hypertension. The ECOG status was 1 in 75% and 2 in 6.3% of patients. Visceral metastasis was seen in 56% of patients, while 37.5% of patients showed brain metastasis. There were 12 (75%) patients with ER or progesterone receptor (PgR)-positive and HER2- positive tumors, and 4 (25%) patients with tumors that were ER-and PgR-negative and HER2-positive. Out of the total patients analyzed, nearly 50% of patients were initially diagnosed at stage 3, followed by 37.5% of patients at stage 4 and 12.5% of patients at stage 2. 10 patients (62.5 %) had involvement of more than two metastatic sites. Nearly 62.5 % of patients presented at stage IV of cancer post-progression from the EBC/LABC category, while 37.5 % of cases had de novo metastatic status at the time of diagnosis [Table 1].

Prior treatments before T-DM1 therapy

Before starting on T-DM1, all study patients received prior trastuzumab-based treatment for metastatic and/or early-stage disease; 12 (75%) patients received anthracyclines, and 15 (93.8%) patients received taxane-based treatment. In the metastatic setting, 1 (6.3%) patient received pertuzumab, 6 (37.5%) patients received capecitabine, and 4 (25%) patients received lapatinib prior to T-DM1 therapy. The data indicates that trastuzumab plus chemotherapy was the first line of treatment for most patients, with T-DM1 being the second line of treatment, as per the approved indication in nearly 31.5% of cases. Five patients (31.5%) received T-DM1 as a first-line treatment due to recurrence as metastasis within six months (of completing adjuvant therapy), and six patients (37.5%) received more than three prior lines of systemic treatment for metastatic disease. Patients were given T-DM1 at a dose of 3.6 mg/kg intravenously every 21 days. Nearly 50% of the patients received more than five treatment cycles with T-DM1. However, 1/3rd of the patients discontinued the treatment due to disease progression. Only 6.25 % of patients, i.e., only one patient each, were reported to discontinue treatment because of financial issues or unmanageable adverse events [Table 2].

Clinical Outcomes

Efficacy

The ORR was observed to be 81.3% in the study population. The Kaplan-Meier curve showed that the median PFS in the study patients was nearly 6 months. 1 (6.3%) of the patients achieved a complete response out of the total observed patients. 12 Patients (75%) achieved a partial response, and three (18.8%)

patients were in a stable disease condition (≥ 6 months) with T-DM1 treatment [Table 3]. Among the 6 patients with CNS metastases, PFS was six months (95% CI: 2.39-9.60) (Figure 1). A partial response was obtained in 5 patients (83.3 %), and they continued the therapy [Table 4].

Table 2: Distribution of study patients based on drug/ therapy

	N	%
Therapy used before T-DM1		
Trastuzumab	16	100.0
Pertuzumab	1	6.3
Lapatinib	4	25.0
Capecitabine	6	37.5
Anthracycline	12	75.0
Taxane	15	93.8
Endocrine Therapy	8	50.0
Radiation therapy for brain metastasis		
Not Applicable	10	62.5
Yes	6	37.5
Total No. of cycles with T-DM1		
≤5	5	31.25
6-10	8	50.0
>10	3	18.75
T-DM1 used in which line		
1	5	31.3
2	5	31.3
3	4	25.0
>=5	2	12.5
Reason for Treatment Discontinuation		
Progression of the disease	5	31.25
Financial issue	1	6.25
Unmanageable adverse event	1	6.25
Lost to follow up	3	18.75
Death	1	6.25
Unknown	5	31.25

Table 3: Distribution of study patients according to Best Response Observed on T-DM1 therapy

	N	%
Complete Response	1	6.3
Partial Response	12	75.0
Stable Disease	3	18.8

Table 4: Characteristics and outcome-related parameters among study patients having brain metastasis

	N	%
Total patients	6	37.5
T-DM1 used in which line		
1	2	33.3
2	2	33.3
3	1	16.7
>=5	1	16.7
Best response obtained		
Complete Response	0	0.0
Partial Response	5	83.3
Stable Disease	1	16.7
PFS Median (Months)	6	

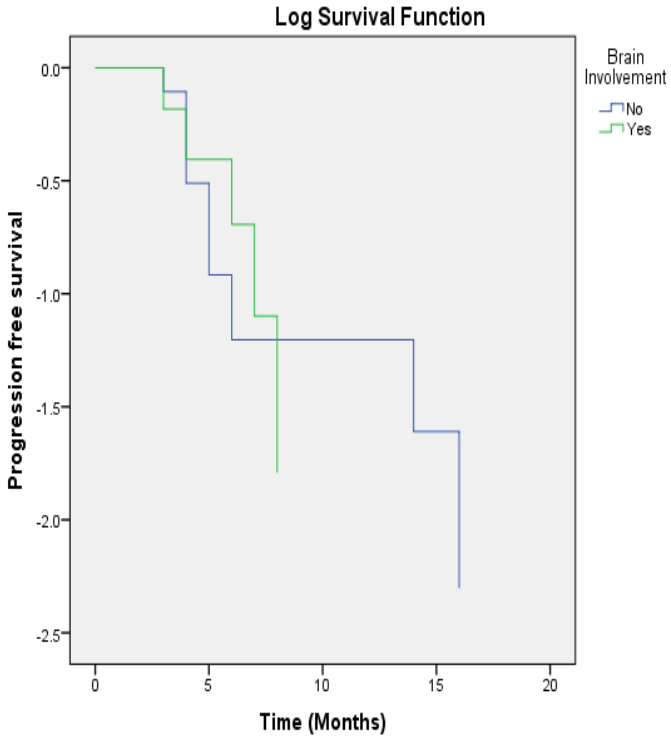

Figure 1: Progression-free survival in patients with and without brain metastasis treated with T-DM1

Safety

Thrombocytopenia (31.25%) and anemia (31.25%) were the most common adverse events recorded by study patients. Neutropenia, hyperglycemia, and weariness (12.5 %) were the subsequent most common adverse events [Table 5]. Two patients (12.5%) had grade 3 thrombocytopenia, while three patients (18.75%) had grade 2-3 tiredness. During or following

T-DM1 treatment, none of the patients suffered grade 3–4 cardiac toxicity. There were no reported cases of asthenia or grade 3–4 neutropenia. Transaminase levels were not elevated by grade 3–4 in any of the individuals, nor were they hyperglycaemic.

Table 5: Frequency distribution of study patients according to adverse events

	Any Grade	Grade 3-4
Elevated Transaminases	1	0
Thrombocytopenia	7	2
Anaemia	6	1
Neutropenia	2	0
LVEF <50%	1	0
Hyperglycaemia	1	0
Asthenia	1	0
Fatigue	3	1

DISCUSSION

We assessed T-DM1's safety and effectiveness in this single-centered study and its effects on a true population of HER2-positive mBC patients. Based on the results of two essential trials, EMILIA [6–8] and TH3RESA, T-DM1 has been recognized as the gold standard of care among the medicines for treating advanced or metastatic HER2-positive breast cancer in patients who have previously received trastuzumab and taxane [8].

The EMILIA and TH3RESA trials are prospective clinical trials evaluating specific treatments in a controlled setting, while this study is a retrospective observational study analyzing real-world data from patients who received treatment outside of a clinical trial setting. It is a challenge to compare the results of clinical trials with those from routine clinical practice, as the patient populations will significantly differ in real-world settings. EMILIA [6,7,9] and TH3RESA [8] are randomized, international, open-label trials conducted on HER2-positive breast cancer patients to independently review the PFS by administering T-DM1 versus Lapatinib plus capecitabine or the physician's choice of drug? The findings of these studies demonstrated that T-DM1, in contrast to other medications such as lapatinib with capecitabine, prolonged both PFS and OS [9,12]. The present study found that patients treated with T-DM1 who were HER2-positive and had CNS involvement had a median PFS of almost six months. This outcome was consistent with the exploratory analysis findings from the EMILIA trial in patients who had baseline CNS metastases (5.9 months) [10]. The EMILIA trial demonstrated a positive effect of T-DM1 on overall survival. However, our study has yet to reach a stage where it can confirm or refute similar findings due to the unavailability of matured overall survival data [8]. Nonetheless, 37.5% of our patients presented with CNS involvement, while CNS involvement in patients of EMILIA and TH3RESA trials was 9% and 10%, respectively.

In addition, 62.5% of patients in the current study had metastases in two or more sites, compared to 37% in the EMILIA study and 64% in the TH3RESA study, where patients had metastases in three or more sites. Interestingly, despite the challenging conditions of CNS involvement and active metastasis in the study patients, there was a favorable response in terms of PFS following treatment with T-DM1. This finding suggests that T-DM1 might be a viable treatment choice, even for patients with HER2-positive breast cancer that is in these complicated and advanced stages.

A total of 109 patients with HER2-positive breast cancer had an incidence of ADC-related mortality rate of 1.00%, according to many studies. Numerous phase 3 studies also revealed that many patients do experience the development of metastatic illness following the completion of adjuvant or neoadjuvant trastuzumab-based therapy, often within a brief disease-free interval of less than six months [13]. Results from HER2-positive breast cancer women in a multivariate model who were on T-DM1 had experienced a 44% decline in the risk of death as compared to other cytotoxic chemotherapeutic agents.

While transaminase levels were elevated in 7.2% of patients in the EMILIA trial, none of this study's patients demonstrated this. Even though 16% of patients in the THERESA trial had neutropenia, there was no indication in this investigation. Thrombocytopenia was seen in 31% of patients in this study, similar to the 32.6% in the EMILIA and 15% in the TH3RESA trial. Although 33.3% of the patients presented with anemia and fatigue in this study, the proportion of patients experiencing anemic symptoms was less in the EMILIA and TH3RESA studies [10,14]. Only one of our study patients was reported with hypokalaemia. In summary, the T-DM1 biosimilar was found to be an effective and well-tolerated therapy in routine clinical practice, which offers a newer therapeutic regimen as an

affordable option, even for heavily pre-treated patients with advanced HER2-positive breast cancer. T-DM1 biosimilar got approval for its clinical use in India by proving its bio similarity and non-inferiority compared to the reference molecule in the phase 3 clinical trial conducted among the Indian cohort [15]. Though PFS and OS were highly dependent on the number of pre-treatments received by patients and other parameters, results obtained in the present study were comparable to those of EMILIA and TH3RESA trials. A major limitation of this study is its small sample size and retrospective design, which may require a larger sample size for increased statistical power to draw definitive conclusions. Additionally, the retrospective nature of the study limits control over data quality. A more extensive study with a more representative sample size would be needed to confirm the findings. Additionally, the study was conducted at a single center, potentially limiting the generalizability of the findings to other healthcare settings.

CONCLUSION

The study shows that T-DM1 benefits patients with HER2-positive metastatic breast cancer in terms of ORR and PFS. The study conducted on this patient group showed excellent safety and tolerability profiles, and the biosimilar T-DM1's real-world data suggests that it may be used routinely in clinical settings to treat breast cancer patients. The availability of the T-DM1 biosimilar in India can positively impact patient outcomes by improving access to treatment, enhancing cost-effectiveness, and maintaining quality of care.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

The Institutional Ethics Committee (8-2-293/82/I/276A) approved the study, and the patient data was retrieved from the hospital's electronic medical record (EMR) system.

ACKNOWLEDGEMENT

The authors express their deepest gratitude to the patients whose data is used to generate these valuable insights. They also thank Dr. Vipulkumar Thummar and Dr. Priya Mehta from the Medical Team of Zydus Lifesciences Ltd. Ahmedabad, India, for their valuable contributions to the study from inception to final publication.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Vindhya Vasini and Mohana Vamsy participated in the design, data collection, and analysis of the data and drafted the manuscript. Monal Dayal and Pavan Shankar performed data collection and data analysis and reviewed the manuscript. All authors read and approved the final manuscript.

REFERENCES

[1] Schlam I, Swain SM. HER2-positive breast cancer and tyrosine kinase inhibitors: the time is now. *NPJ Breast Cancer*, **7**, 56 (2021).

[2] Hu XE, Yang P, Chen S, Wei G, Yuan L, Yang Z, Gong L, He L, Yang L, Peng S, Dong Y, He X, Bao G. Clinical and biological heterogeneities in triple-negative breast cancer reveals a non-negligible role of HER2-low. *Breast Cancer Res*, **25**, 34 (2023).

[3] WHO launches new roadmap on breast cancer [Internet]. [cited 2024 Mar 31]. Available from: https://www.who.int/news/item/03-02-2023-who-launches-new-roadmap-on-breast-cancer

[4] Mercogliano MF, Bruni S, Mauro FL, Schillaci R. Emerging Targeted Therapies for HER2-Positive Breast Cancer. *Cancers (Basel)*, **15**, 1987 (2023).

[5] Gajria D, Chandarlapaty S. HER2-amplified breast cancer: mechanisms of trastuzumab resistance and novel targeted therapies. *Expert Rev Anticancer Ther*, **11**, 263 (2011).

[6] Understanding Your Breast Cancer Diagnosis | American Cancer Society [Internet]. [cited 2024 Feb 6]. Available from: https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis.html

[7] Jankowitz RC, Brufsky AM. Adjuvant treatment of HER2-positive breast cancer: winning efforts continue to improve HER2-positive patient outcome long-term. *Breast Cancer Res*, **14**, 308 (2012).

[8] Hardy-Werbin M, Quiroga V, Cirauqui B, Romeo M, Felip E, Teruel I, Garcia JJ, Erasun C, España S, Cucurull M, Montprade E, Pardo JC, Carballo D, Velarde JM, Margeli M. Real-world data on T-DM1 efficacy - results of a single-center retrospective study of HER2-positive breast cancer patients. *Sci Rep*, **9**, 12760 (2019).

[9] Thukral DG, Thummar DV, Mehta DP, Janagama DV, Khambhati K. Drug Utilization Pattern of World's First T-DM1 Biosimilar (UJVIRATM) For Her2+ Breast Cancer in First Year of Its Availability – An Indian Context. *Int J Med Sci Clin Invent*, **10**, 6561–8 (2023).

[10] Krop IE, Lin NU, Blackwell K, Guardino E, Huober J, Lu M, Miles D, Samant M, Welslau M, Diéras V. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: A retrospective, exploratory analysis in EMILIA. *Annals of Oncology*, **26**, 113–9 (2015).

[11] Schneider BP, O'Neill A, Shen F, Sledge GW, Thor AD, Kahanic SP, Zander PJ, Davidson NE. Pilot trial of paclitaxel-trastuzumab adjuvant therapy for early stage breast cancer: A trial of the ECOG-ACRIN cancer research group (E2198). *Br J Cancer*, **113**, 1651–7 (2015).

[12] Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh D-Y, Diéras V, Guardino E, Fang L, Lu MW, Olsen S, Blackwell K. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. *New England Journal of Medicine*, **367**, 1783–91 (2012).

[13] Fu Z, Liu J, Li S, Shi C, Zhang Y. Treatment-related adverse events associated with HER2-Targeted antibody-drug conjugates in clinical trials: a systematic review and meta-analysis. *EClinicalMedicine*, **55**, 101795 (2023).

[14] Krop IE, Kim S-B, González-Martín A, LoRusso PM, Ferrero J-M, Smitt M, Yu R, Leung ACF, Wildiers H. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol*, **15**, 689–99 (2014).

[15] Chiradoni Thungappa S, Maksud T, Raut N, Nagarkar R, Batra U, Kumar S, Parmar D. Comparison of the Efficacy, Safety, Pharmacokinetic and Immunogenicity of UJVIRA (ZRC-3256, Trastuzumab Emtansine) With the Kadcyla (Trastuzumab Emtansine) in the Treatment of HER2-Positive Metastatic Breast Cancer: A Randomized, Open-Label, Multicenter Study in India. *Clin Breast Cancer*, **22**, 300–7 (2022).