JMSCR Volume||2||Issue||5||Page 1222-1234||May 2014 2014

www.jmscr.igmpublication.org Impact Factor-1.1147
ISSN (e)-2347-176x

Journal Of Medical Science And Clinical Research
IGM Publication An Official Publication Of IGM Publication

Meta-Analysis of Ado-Trastuzumab Emtansine in Patients with HER2-Positive Advanced Metastatic Breast Cancer

Authors

Dr Rajat Rana[1], Sappa Dilip Kumar[2], Dr Soumadip Das[3], Dr Aravinda Swami[4] Dr Doreen Pon[5], Dr K K Perumal [6]

[1]Doctor of Pharmacy (Pharm.D), R.M Medical College & Hospital
Annamalai University, India 608002
[2]Pharm D, R.M Medical College & Hospital, Annamalai University, India
[3]Doctor of Pharmacy (Pharm.D), R.M Medical College & Hospital
Annamalai University, India
[4]Doctor of Pharmacy (Pharm.D), R.M Medical College & Hospital
Annamalai University, India
[5]Assistant Professor, Pharm.D, BCOP, Pharmacy Practice and Administration
College of Pharmacy Western University, California, US
[6]Professor, M.D, R.M Medical College & Hospital
Annamalai University, India
Emails: *rajatrana91@gmail.com, sappadilipkumar@gmail.com, soumadipdas90@gmail.com, swami8055@gmail.com, d.pon.@westernu.edu, perumal.med@gmail.com*

Corresponding Author
Dr Rajat Rana
Doctor of Pharmacy (Pharm.D)
R.M Medical College & Hospital, Annamalai University
India 608002
Email: *rajatrana91@gmail.com*

Abstract
This study identifies and reviews randomized evidence to determine the effectiveness and safety of Ado-Trastuzumab Emtansine in patients with advanced metastatic breast cancer. Cochrane Breast Cancer Group specialized register; Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL and WHO International Clinical Registry platform were searched using the appropriate search strategy. Either recurrent or newly diagnosed women with Metastatic Breast Cancer were included. Four randomized controlled trials with 1,350 patients estimated overall survival as 64.7% in TDM1 group versus 51.8% in non TDM1 group. EMILIA study reported improved progression free survival (PFS) by 5.8 months, Overall Response Rate (ORR) as 43.6% in TDM1 group vs. 30.8% control group and low adverse events by 16.2%. Hurvitz study reported PFS 5 months longer in T-DM1 group than in control group with stratified HR of 0.59;(95% CI, 0.36 to 0.97), ORR as 64.2% (TDM 1 group) vs. 58% in control group, low adverse events by 45.2%. Single arm phase II study BURRIS & KROP reported PFS as 4.6 and 6.9 months respectively, ORR 25.9% and 34.5% respectively, and adverse events as 15.2% and 55.4% respectively. Consistent favorable outcomes with the Ado-Trastuzumab Emtansine indicate its considerable efficacy and safety in the treatment of advanced metastatic breast cancer and promising drug in combating mortality with breast cancer.
Keywords: Ado-Trastuzumab Emtansine, metastatic breast cancer, overall survival, Objective Response rate, progression free survival

INTRODUCTION

Breast cancer accounts for nearly 1 in 3 cancer diagnoses in women in the U.S. Among women, it is the most common cancer after non-melanoma skin cancer. After lung cancer, breast cancer ranks second for cancer mortality. [(1)] In 2013, it is estimated around 39,620 breast cancer related deaths among women in the United States.[(2)] and 88,886 in Europe.[(3)] Metastatic breast cancer has a poor prognosis and incurable in advanced metastasis. Amplification of human epidermal growth factor receptor 2 (HER2, also called ErbB2) occurs in approximately 20% of breast cancers and is associated with shortened Survival. Ado-Trastuzumab Emtansine is an antibody-drug conjugate comprising Trastuzumab and Emtansine (previously called "DM1" for "derivative of maytansine 1") is a sulfur-containing derivative of the potent microtubule inhibitor, maytansine. Emtansine is conjugated to Trastuzumab by lysine side chains, Emtansine the conjugate also seems to maintain the antitumor activity of Trastuzumab forming a stable thioether linker. [(4)] Once internalized, proteolytic degradation of the linker releases both Trastuzumab and the active metabolite, maleimidomethyl cyclohexane-1-carboxylate (MCC)-Emtansine. MCC-Emtansine contains both positive and negative charges and therefore does not readily cross plasma membranes, maintaining intracellular concentrations.[(5)]

OBJECTIVES

This study was aimed with the primary objective to determine the outcomes of Ado-Trastuzumab Emtansine containing therapy in terms of survival, efficacy and safety in the treatment of patients with advanced metastatic breast cancer.

METHODS

Criteria for considering studies for this review was randomized control trials that access the overall effectiveness, safety and response of Ado-Trastuzumab Emtansine in patients with advance Metastatic Breast Cancer. The studies could be double blinded, single blinded or unblinded, single arm or double arm. Either recurrent or newly diagnosed women with definite evidence of Advanced Metastatic Breast Cancer were included. There were no restrictions on age, estrogen receptors, metastatic site of the patient included. The highly specific patient groups such as pregnant women and pediatric population were excluded. The intervention was assigned as any Ado-Trastuzumab Emtansine containing regimen compared to non-Ado-Trastuzumab Emtansine containing regimen. All the randomized control trials investigating the role of Ado-Trastuzumab Emtansine in population with advanced Metastatic Breast Cancer were included.

Outcome measures were Progression Free Survival (PFS) defined as the time from randomization to progression or death from any cause. Progression was assessed according to modified Response Evaluation Criteria in Solid Tumors (RECIST) [13], version 1.0; by independent review. Overall survival (OS) defined as the time from Randomization to death from any cause. Objective Response Rate (ORR) was defined as the proportion of patients with either complete or partial shrinkage of tumors. It was assessed according to modified RECIST [13] on the basis of the independent review of patients with measurable disease at baseline. Toxicity, the adverse events were monitored continuously and graded according to the CTCAE, version 3.0[12].

MEDLINE (2001 to September 2013) using the advance search strategy. A thorough search of all indexed and non-indexed fields for the study was applied according to the code references. A further search was carried out in the Cochrane Central Register of Controlled Trials (CENTRAL) until 2013 (issue 10 of 12, September 2013). This register includes both published and unpublished (including ongoing) trials, in addition EMBASE (1998 to august 2013), CINAHL (1982 to September 2013), WHO International Clinical Registry platform search portal (September 2013) were searched. The Cochrane Breast Cancer Group specialized register (CBCG) (issue 9 of 12, September 2013) was searched with the search strategy used by the group to create the register. Various other resources such as reference actions of each published papers, conference proceedings and hand searches were searched for the data. There were no linguistic restrictions imposed on our searching activities.

Data Collection and Analyses

Study selection was undertaken independently two of the authors (RR, SD) both of whom are content experts. The data was extracted independently by the two authors. When possible, the HR was extracted from the trial publication(s). If not reported it was obtained indirectly through the methods described by Parmar et.al using either

other available summary statistics or from the data extracted from published Kaplan-Meier curves [10]. A weighted average of survival duration across studies was then calculated. The pooled HR was obtained by combining the observed (O) minus the expected (E) number of events and the variance for each trial using the fixed effect model [14].

Objective response rate (ORR) was analyzed as dichotomous variables and were obtained from the tables of best response presented for each trial and pooled relative risk was derived. Randomized response as reported by the trialist was used for statistical analysis. Toxicity data were extracted and total number of grade 3 or above adverse events were used to calculate the possible odds ratio. The total number of toxic events was extracted for frequent events like Hypokalemia, thrombocytopenia and fatigue which were all rated equal or above grade 3 according to the CTCAE version3.0 [12]. The statistical heterogeneity was assessed using I^2 test where a value greater than 50% indicated substantial heterogeneity [9]. Aggregate data methods [10, 11] were employed for time to event outcomes in the first instance and results were presented as Hazard ratios with 95% CI. Evidence of heterogeneity between trials were identified for tumor response rates and adverse events. Since the data from uncontrolled trial [6, 7] was not sufficient to estimate the overall heterogeneity among the trials, the odds ratio was not estimable.

RESULTS

All of the identified trials were Randomized control studies conducted on patients with Advanced Metastatic Breast Cancer treated with Ado-Trastuzumab Emtansine. Four eligible control trials were included in the analysis representing total of 1,350 participants (Table 1). 20 of RCT records were identified through database searching, additional five similar study records were identified through the other sources. After screening of 23 records 12 were excluded. 11 full text articles were assessed for eligibility out of which 7 were excluded since, their noncompliance to the predefined inclusion criteria this resulted in four Randomized Control Trials to be included in quantitative synthesis of the data. Many controlled trials were excluded since, they are ongoing trials or unpublished trials. (Fig 1).

We included four trials which Randomized 1,350 patients. There was a great deal of variation across the trials ranging from 991[4] to 110[6]. Of the four identified Randomized Control Trials two of them were controlled studies comparing the overall effect of Ado-Trastuzumab Emtansine comparing in experimental and study group. The approval of the Ado-Trastuzumab Emtansine (T-DM1) in February 2013 by USFDA was based on the prospective double blinded clinical trial EMILIA study group [4] for women with advanced HER2 positive breast cancer who are already resistant to Trastuzumab alone it improved, survival by 5.8 months compared to the combination Lapatinib

and Capecitabine the follow-up period for this study was 19 months.

Another trial Hurvitz [8] et.al was Randomized study of Trastuzumab Emtansine versus Trastuzumab plus Docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer with total 137 participants the follow-up period for this study was equal or greater than 14.2 months. Further two eligible two trials were selected based upon predefined inclusion criteria. KROP et.al was single arm phase II study of Trastuzumab Emtansine in 110 patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with Trastuzumab, lapatinib, and anthracycline, a taxane and Capecitabine with the median follow-up period of 19 months. Another single arm phase II study Burris [7] et.al studied antibody drug conjugate T-DM1 for the treatment of HER2-positive breast cancer after prior HER2 directed therapy in 112 total participants with a median follow-up period of 12 or more months. In all the four trials T-DM1 was used in the participants although the data from double arm studies and single arm studies could not be calculated as single variable in terms of Hazard ratio or odds ratio. Data for all the end points were not available in the published reports.

A total of 1,350 participants were randomized in the four included trials the ratio of treatment defects are reported in terms of relative risk(RR), Hazard ratio(HR), odds ratio as applicable for comparison between the groups with the use of Mantel-Haenszel (MH) Chi-square with stratification according to the factors used for randomization for patients with objective response progression free survival and overall survival were analyzed by independent review with the use of Kaplan-Meier approach.

Overall survival Data on overall survival was extracted from one trial [4] (EMILIA study group) out of all the four trials, since the survival and time to event data was available with the high grade evidence only for the EMILIA 2012 trial. The data obtained from other trials was insufficient and under reported to come up to a definite conclusion (Fig2).

The reported data in EMILIA study group was assessed as intention to treat population and tested by means of two sided log rank test, with stratification according to the factors for randomization Kaplan-Meier methods were used to estimate medians for survival rate with 95% CI. The analysis of overall survival (331) deaths, estimated one year survival rate as 85.2% (95% CI, 0.55 to 0.85; P<0.001) in the T-DM1 group and 78.4% (95% CI, 74.6 to 82.3) in the lapatinib plus Capecitabine group. The overall survival rate at two year was 64.7% (95% CI, 59.3 to 70.2) and 51.8% (95% CI, 45.9 to 57.7) in T-DM1 and lapatinib plus Capecitabine respectively. The overall survival of this study met the predefined O'BRIEN-FLEMING stopping boundary. Data in this trial significantly supported superiority of T-DM1 over the non T-DM1 therapy statistically.

Progression free survival Data on progression was available for four trials in 1,350 randomly assigned patients with Metastatic Breast Cancer. Overall median progression free survival assessed by independent review was calculated as 5.6 months for the subjects treated with Ado-Trastuzumab Emtansine which was significantly superior when compared to the subjects with non T-DM1 therapy.

The EMILIA study reported an improved survival by 5.8 months compared to the combination of lapatinib plus Capecitabine. The first interim analysis of progression free survival was estimated 3.2 months longer in Trastuzumab Emtansine than in lapatinib Capecitabine group. The study group with T-DM1 showed 9.6 months progression free survival compared to 6.4 months in lapatinib Capecitabine group. The stratified hazard ratio for death from any cause with T-DM1 vs. lapatinib plus Capecitabine was 0.62 (95% CI, 0.482 to 0.81; p=0.0005) and did not cross the predefined O'BRIEN-FLEMINGS stopping boundary (P=0.0003). The second interim analysis of progression free survival estimated that T-DM1 significantly increased the overall survival by 5.8 months (30.9 months vs. 25.1 months for lapatinib Capecitabine group) with stratified hazard ratio for death from any cause 0.68 (95% CI, 0.55 to 0.85; P<0.001). (Fig 3)

Another study Hurvitz et.al [8] was phase II randomized study of Trastuzumab Emtansine versus Trastuzumab plus Docetaxel in 137 patients with HER2-positive metastatic breast cancer. The median progression free survival was 5 months longer T-DM1 group than in Trastuzumab plus Docetaxel group (14.2 months vs. 9.2 months for non T-DM1 group) with stratified hazard ratio of 0.59;(95% CI, 0.36 to 0.97); (Table. 1) in this study the treatment group T-DM1 with HER2-postive MBC provided a significant improvement in PFS with statistically significant superiority. A single arm phase II study Burris et.al[7] studied Trastuzumab-DM1 for the treatment of HER2- positive metastatic after prior HER2 directed therapy in 112 randomly assigned participants. A significant improved median progression free survival was estimated as 4.6 months (95% CI, 3.9 to 8.6 months) which supported high grade evidence of superiority of Trastuzumab-DM1 for the treatment of HER2-positive breast cancer. Another single arm phase II study Krop et.al[6] studied Trastuzumab Emtansine in patients with HER2-positive metastatic breast cancer over previously treated with Trastuzumab, Lapatinib an anthracycline, taxane, and Capecitabine among 110 randomly assigned patients the median progression free survival was 6.9 months (95% CI, 4.2 to 8.4 months) (Table 1) indicating statistically significant improvement in progression free survival of patient with HER2-positive metastatic breast cancer treated with Trastuzumab Emtansine (T-DM1) suggesting high single agent activity in patients.

Objective Response Rate Data on objective response rate were available on four trials in 1,350

randomly assigned patients with metastatic breast cancer. All the trials documented significant superiority of T-DM1for high objective response rate. The EMILIA study demonstrated 12.8% higher objective response rate in subjects treated with T-DM1 compared to the subjects treated with lapatinib plus Capecitabine. The objective response rate in the study group with T-DM1 was estimated as 43.6% (95% CI, 38.6%to 48.6%) where as the control group with lapatinib plus Capecitabine reported 30.8% (95% CI, 26.3 to 35.7; P<0.001) (Table 1) which showed a statistical significant advantage of T-DM1 in high objective response rate (ORR) compared to lapatinib plus Capecitabine group. The Hurvitz et al study demonstrated 6.2% higher objective response rate in subjects treated with T-DM1 compared to the subjects treated with Trastuzumab plus Docetaxel. The objective response rate in the study group with T-DM1 was estimated as 64.2% (95% CI, 51.8% to 74.8%) where as the control group with Trastuzumab plus Docetaxel reported 58% (95% CI, 45.5% to 69.2%) which showed a statistical significant advantage of T-DM1 in high objective response rate (ORR) compared to Trastuzumab plus Docetaxel group. In two trials (EMILIA study group; Hurvitz et.al) [4, 8] the risk ratio M-H, fixed, 95% CI was estimated as 1.33[1.14, 1.56] which statistically favored T-DM1for a significant objective response rate. The EMILIA study group estimated a risk ratio of 1.41 [95% CI, M-H fixed 1.17, 1.70] whereas Hurvitz study group reported a risk ratio of 1.10 [95% CI, M-H fixed 0.84, 1.43]. The statistical heterogeneity was Chi^2 equals to 2.46, df=1 (P=0.12); I^2=59%. The test for overall effect for these two trials was calculated as Z=3.62 (P=0.0003) (fig 4).

Another two single arm randomized trials Krop et.al[6] and Burris et.al[7] reported objective response rate 34.5% (95% CI, 26.1% to 43.9%) and 25.9% (95% CI, 18.4% to 34.4%) respectively by independent assessment both suggesting a higher objective response rate in patients with HER2-positive advanced metastatic breast cancer treated with Trastuzumab Emtansine (T-DM1). The statistical heterogeneity and sensitivity analysis was not estimable since it was a single arm study with insufficient data required for the analysis.

In Toxicity there was limited information available from the trials included on toxicity profile. All the four published trials commented on frequent adverse events graded more than 3according to CTCAE version3.0 and decisively supported superior safety profile of T-DM1 in metastatic breast cancer.

In the study conducted by EMILIA study group the rates of adverse events of grade 3 or above were higher with lapatinib plus Capecitabine than with T-DM1 (57% vs. 40.8%). The incidences of thrombocytopenia (0.2% vs12.9%), an increased amino transferase levels (0.8% vs. 4.3%), increased ALT levels (1.4% vs. 2.9%) and anemia (1.6% vs. 2.7%) were recorded for lapatinib plus Capecitabine group versus T-DM1 in which T-

DM1 had higher adverse events compared to non T-DM1 group. The incidences of diarrhea(20.7% vs. 1.6%) nausea(2.5% vs. 0.8%) vomiting(4.5% vs. 0.8%), neutropenia (4.3% vs. 0.2%), hypokalemia (4.1% vs. 2.2%) and Palmar-Plantar Erythrodysesthesia (16.4% vs. 0%)(Fig 5) were recorded for lapatinib plus Capecitabine group versus T-DM1 in which lapatinib plus Capecitabine group had higher adverse events compared to T-DM1 group. Another study Hurvitz et al reported that T-DM1 had favorable safety profile versus Trastuzumab plus Docetaxel group, with fewer grade ≥3 adverse events (adverse events; 46.2% in T-DM1 group versus 91.4% in Trastuzumab plus Docetaxel group. Adverse events leading to treatment discontinuations (7.2%for T-DM1 vs. 40.9% in control group) and serious adverse events (20.3% in T-DM1 group vs. 25.8% in control group) which conclusively supported the high safety profile and low toxicity of T-DM1 compared to Trastuzumab plus Docetaxel regimen. In two trials [4,8] (EMILIA study group; Hurvitz et al) the odds ratio M-H, fixed, 95% CI was estimated as 0.45[0.35, 0.57] which statistically favored T-DM1for a significant low toxicity profile. The EMILIA 2012 study group estimated odds ratio of 0.53 [95% CI, M-H fixed 0.40, 0.67] whereas Hurvitz et al study group reported odds ratio of 0.08 [95% CI, M-H fixed 0.03, 0.21]. The statistical heterogeneity was Chi^2 equals to 13.49, df=1 (P=0.0002); I^2=93%. The test for overall effect for these two trials was calculated as Z=5.56 (P<0.00001).

Table 1 Summary of Findings

<table>
<tr><td></td><td>Total Participants</td><td colspan="2">Progression free Survival (PFS)</td><td colspan="4">Objective Response Rate (ORR)</td><td colspan="4">SAFETY (Adverse events) ≥ GRADE 3</td><td colspan="2">Overall Survival (OS)</td></tr>
<tr><td></td><td rowspan="2">1350</td><td rowspan="2">T-DM1</td><td rowspan="2">Non T-DM1</td><td colspan="2">T-DM1</td><td colspan="2">Non T-DM1</td><td colspan="2">T-DM1</td><td colspan="2">Non T-DM1</td><td></td><td></td></tr>
<tr><td></td><td>n</td><td>N</td><td>n</td><td>N</td><td>n</td><td>N</td><td>n</td><td>N</td><td>n</td><td>N</td></tr>
<tr><td rowspan="3">EMILIA</td><td rowspan="3">991</td><td>30.9 Months</td><td>25.1 Months</td><td rowspan="2">173</td><td rowspan="2">397</td><td rowspan="2">120</td><td rowspan="2">389</td><td rowspan="2">200</td><td rowspan="2">490</td><td rowspan="2">278</td><td rowspan="2">488</td><td rowspan="2">64.7% 95% CI, 59.3 to 70.2</td><td rowspan="2">51.8% (95% CI, 45.9 to 57.7)</td></tr>
<tr><td colspan="2" rowspan="2">0.68 (95% CI, 0.55 to 0.85; P<0.001) Stratified Hazard ratio</td></tr>
<tr><td colspan="2">43.6%; 95% CI, 38.6 to 48.6</td><td colspan="2">30.8%; 95% CI, 26.3 to 35.7;p<0.001</td><td colspan="2">40.8%</td><td colspan="2">57%</td><td colspan="2">No of deaths 331</td></tr>
</table>

HURVITZ	137	14.2 months	9.2 months	43	67	41	70	31	67	64	70		
		0.59; 95% CI, 0.36 to 0.97) Stratified Hazard ratio		64.2% (95% CI, 51.8% to 74.8%)		58.0% (95% CI, 45.5% to 69.2%)		46.2%		91.4%			
KROP	110	6.9 months (95% CI, 4.2 to 8.4 Months)		38	110			61	110				
				34.5% (95% CI, 26.1% to 43.9%)				55.4%					
BURRIS	112	4.6 months (95% CI, 3.9 to 8.6 months)		29	112			17	112				
				25.9% (95% CI, 18.4% to 34.4%				15.2%					

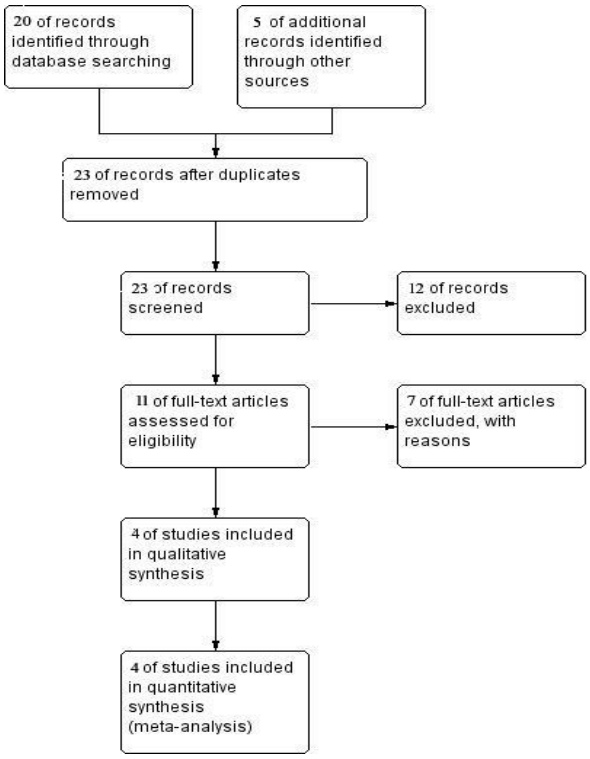

Figure.1- Study Flow Diagram

Median follow-up was 18.6 months (range, 0 to 41) in the lapatinib–capecitabine group and 19.1 months (range, 0 to 40) in the T-DM1 group (EMILIA 2012)

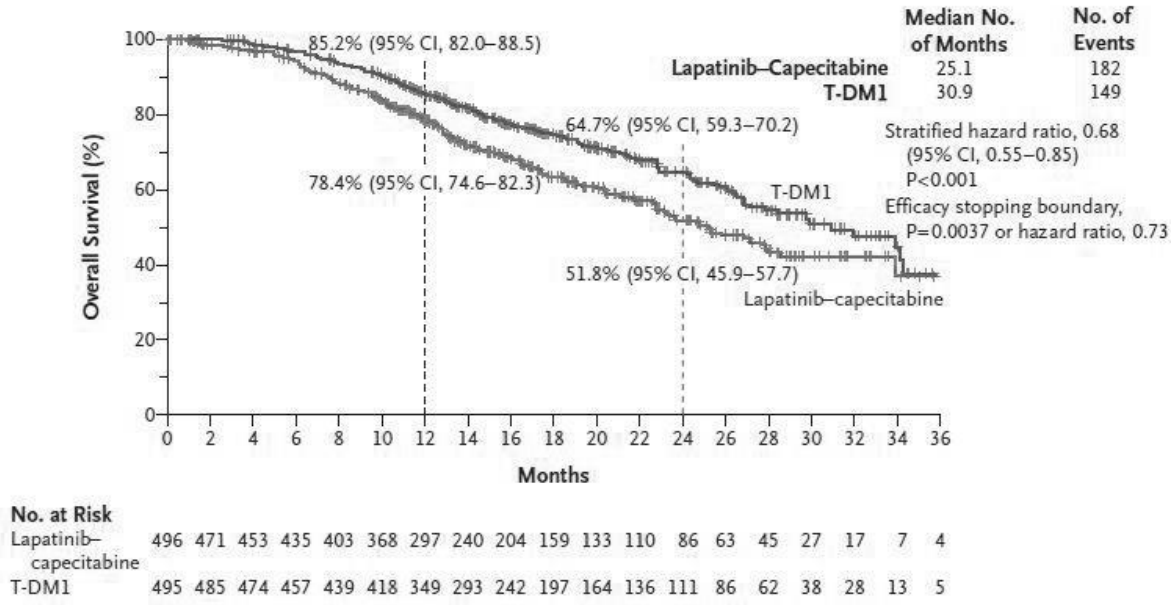

Figure 2- Kaplan–Meier estimates of overall survival Overall Survival

(Reproduced by kind permission *Verma S, Miles D, Gianni L* from *Trastuzumab Emtansine for HER2-positive advanced breast cancer.(EMILIA) group, N Engl J Med 2012; 367(19):1783-91)*

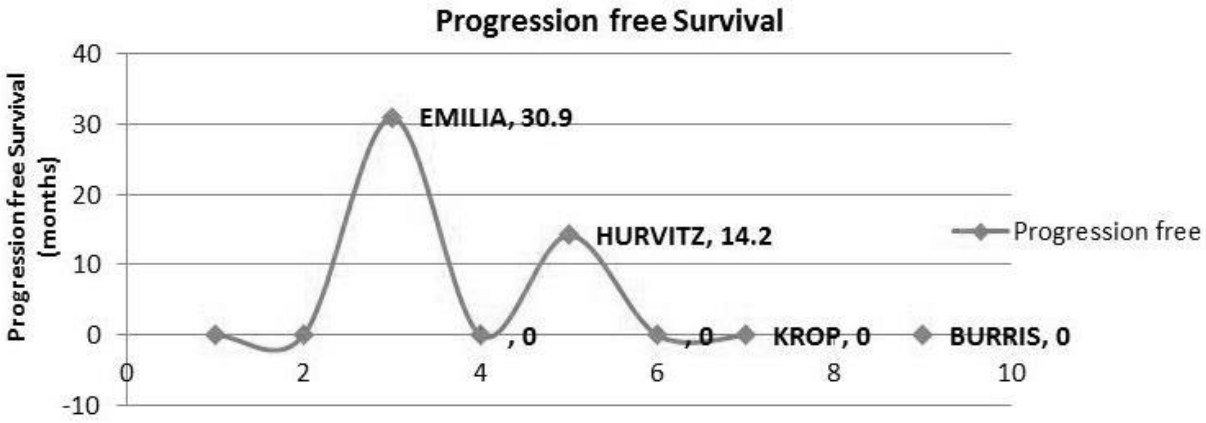

Figure 3-Progression free Survival of included trials

Figure 4 Overall Effects of Ado-Trastuzumab Emtansine, outcome: Objective Response Rate

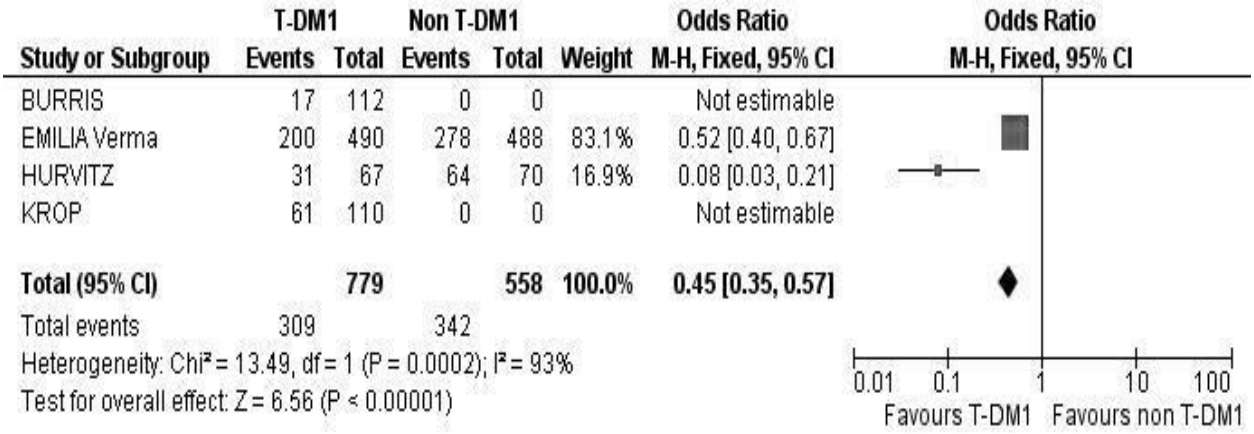

Figure 5 Overall Effects of Ado-Trastuzumab Emtansine, outcome: Adverse Events more than Grade 3

DISCUSSION

This interventional review demonstrates significantly improved progression free survival and overall survival among patients with HER2-metastatic breast cancer for the antibody-drug conjugate Ado-Trastuzumab Emtansine. In terms of progression free survival there was a statistically significant decrease in hazard of progression for treatment with Ado-Trastuzumab Emtansine. On an overall all the included trials indicate benefit with Ado-Trastuzumab Emtansine with the significant overall response rate and low toxicity profile. The consistent and favorable outcomes with the Ado-Trastuzumab Emtansine with regard to the primary and secondary points indicate that Ado-Trastuzumab Emtansine has efficacy in the treatment of HER2-positive advanced metastatic breast cancer. The adverse events associated with Ado-Trastuzumab Emtansine were generally low grade and well tolerated in the subjects. In conclusion our study shows that Ado-Trastuzumab Emtansine has therapeutic potential across the heterogeneous population of patients for the treatment of advanced metastatic breast cancer.

CONCLUSION

When all the trials are considered, this interventional review confirms the improved overall survival, progression free survival, objective response rate, and safety with the use of Ado-Trastuzumab Emtansine in patients with advanced metastatic breast cancer and recommends its implications in clinical practice. Comprehensive follow-up of the ongoing trials is vital and there is need of further trials to standardize reporting of overall survival and toxicity profile of the drug.

Declarations of Interest

None known

ACKNOWLEDGEMENTS:

Dr Daniel Robinson, Pharm.D, FASHP, Dean, College of Pharmacy, Western University of Health Sciences for his guidance and motivation.

REFERENCES

1. Carlson, R. W., et al. "Metastatic breast cancer, version 1.2012: featured updates to the NCCN guidelines." J Natl Compr Canc Netw 10(7): 821-829
2. Cancer Facts & Figures, 2013. Atlanta, GA: American Cancer Society 2013.
3. Malvezzi, M., et al. "European cancer mortality predictions for the year 2013." Ann Oncol 24(3): 792-800.
4. Verma, S., et al. "Trastuzumab emtansine for HER2-positive advanced breast cancer." N Engl J Med 367(19): 1783-1791
5. LoRusso PM, Weiss D, Guardino E et al. "Trastuzumab emtansine: a unique antibody-drug conjugate in development for human epidermal growth factor receptor 2-positive cancer." Clin Cancer Res 2011; 17(20):6437-47.
6. Krop, I. E., et al. "A phase II study of trastuzumab emtansine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine." J Clin Oncol 30(26): 3234-3241.
7. Burris, H. A., 3rd, et al. "Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy." J Clin Oncol 29(4): 398-405.
8. Hurvitz, S. A., et al. "Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer." J Clin Oncol 31(9): 1157-1163
9. JPT Higgins. "Measuring inconsistency in meta-analyses" BMJ 2003; 327:557
10. Parmar, M. K., et al. (1998). "Extracting summary statistics to perform meta-analyses of the published literature for

survival endpoints." Stat Med 17(24): 2815-2834.

11. Williamson, G. R. and S. Prosser (2002). "Action research: politics, ethics and participation." J Adv Nurs 40(5): 587-593.
12. Trotti, A., et al. (2003). "CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment." Semin Radiat Oncol 13(3): 176-181.
13. Eisenhauer, E. A., et al. (2009). "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." Eur J Cancer 45(2): 228-247.
14. Yusuf, S., et al. (1985). "Beta blockade during and after myocardial infarction: an overview of the randomized trials." Prog Cardiovasc Dis 27(5): 335-371.