Short Communication

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Comparative effectiveness of trastuzumab emtansine versus lapatinib plus chemotherapy for HER2+ metastatic breast cancer

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Aim: To investigate the comparative effectiveness of trastuzumab emtansine (T-DM1) in a real-world population of HER2+ metastatic breast cancer (mBC) patients. **Materials & methods:** The Flatiron Health database was used to identify a cohort of HER2+ mBC patients who received first-line trastuzumab treatment and T-DM1 or lapatinib plus chemotherapy as second-line treatment. Overall survival was compared between the two groups. **Results:** A total of 278 patients with HER2+ mBC received second-line T-DM1 and 34 lapatinib plus chemotherapy. Overall survival was longer in patients treated with T-DM1 than those treated with lapatinib plus chemotherapy (adjusted hazard ratio: 0.56; 95% CI: 0.38–0.85). **Conclusion:** Real-world data supports the effectiveness of T-DM1 in the second-line treatment of HER2+ mBC patients.

Lay abstract: EMILIA was a randomized clinical trial (RCT) – a type of study designed to test whether a treatment works in a particular disease, using methods to remove possible bias. The study showed that a treatment called trastuzumab emtansine (shortened to T-DM1) improved the survival of patients with a particular type of breast cancer, known as HER2+ metastatic breast cancer (mBC). However, as clinical trials are run under controlled conditions, they do not fully reflect results under normal circumstances. In this study, we looked at the effect of treating a 'real' population of HER2+ mBC patients with T-DM1 in the USA. We found that T-DM1 still improved survival in these 'real-world' patients. Studies in the 'real world' can have some bias, as they are not controlled like RCTs; however, taking the results of the EMILIA RCT, along with the results of our study, supports the use of T-DM1 as a treatment option for HER2+ mBC patients.

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Keywords: ado-trastuzumab emtansine • breast cancer • chemotherapy • comparative effectiveness research • lapatinib • survival

Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate that incorporates the HER2-targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1. The EMILIA Phase III trial, assessed the efficacy and safety of T-DM1, as compared with lapatinib plus chemotherapy, in patients with HER2-positive (HER2+) advanced breast cancer (BC) previously treated with trastuzumab and a taxane [1]. In the second interim analysis of the EMILIA trial, median overall survival (OS) was 30.9 months for T-DM1 as compared with 25.1 months for lapatinib plus chemotherapy; yielding a hazard ratio (HR) for death from any cause of 0.68 (95% CI: 0.55–0.85) [1].

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The positive results from the EMILIA trial led to the regulatory approval and subsequent widespread use of T-DM1 in HER2+ metastatic BC (mBC). While final results from EMILIA have since confirmed the efficacy of T-DM1 over longer term follow-up [2], few studies have explored the realization of these benefits of T-DM1 in broader real-world populations. The aim of the current study was therefore to compare the real-world effectiveness of T-DM1 to lapatinib plus chemotherapy in second-line treatment of mBC using a longitudinal Electronic Health Record database compiling information from oncology practices in the US.

Materials & methods

Flatiron Health (FH) includes information from more than 265 cancer clinics across the US [3]. Data are deidentified thereby protecting patient confidentiality. Research with the database was approved by the Copernicus Group Institutional Review Board. For this study, data from 1 January 2011, through 31 July 2020, were included for patients with a confirmed diagnosis of mBC and documentation of a positive HER2 test result who were aged 18 or over at time of treatment initiation. Patients had to receive T-DM1 or lapatinib plus chemotherapy for second-line treatment of mBC, with the first line of therapy needing to be trastuzumab based. Patients had to have one or more clinic encounters occurring after initiation of second-line treatment.

Data on key baseline demographic and clinical characteristics were extracted from FH for the study population. Eastern Cooperative Oncology Group (ECOG) performance status assessments recorded following the start of first-line treatment and on or before the start of second-line treatment were used. Where there was more than one value, the maximum value was used. In defining a patient's primary payer, the insurance payer that had a start date prior to and overlapping with the diagnosis of metastatic disease was used. If a patient had more than one payer that met the criteria, the following hierarchy was used to classify a patient: commercial health plan >Medicare >Medicaid >other government plan >patient assistance program >workers compensation >self pay. A patient was considered to have had a diagnosis of metastasis to a given site (bone, lung, liver, brain/central nervous system [CNS]) if the date of diagnosis (to a given site) occurred between the month of metastatic diagnosis and the month of second-line treatment initiation (inclusive). Each independent site of metastasis was used as a separate incident; therefore, a patient could have more than 1 site of metastasis. The number of metastatic sites was the sum of all incidences of metastatic sites identified. Visceral disease was defined as disease with lung, liver or brain metastases. The individual components of the Charlson comorbidity index with the exception of metastatic cancer, were extracted for each patient. A patient was considered to have a diagnosis of a given comorbidity if there was documentation of the diagnosis recorded at any time prior to initiation of second-line treatment, inclusive. First-line and second-line mBC treatments were identified using the derived line of treatment variables that are available in the FH dataset. These derived variables utilize an algorithm to define the timing and constituents of each line of treatment based on the raw treatment data available in the dataset. Time between first-line and second-line treatment initiation was calculated using the start dates of these treatment lines.

Baseline patient demographic and clinical characteristics were summarized using descriptive statistics. OS was defined as the time from initiation of second-line mBC treatment to death from any cause; otherwise, patients were censored at their last visit. The Kaplan–Meier method was used to evaluate median OS. To correct for potential covariate imbalances, all variables listed in Table 1 were considered for inclusion in a logistic regression model to estimate propensity scores. In line with best practice, we sought to construct a propensity score model which included all covariates that were associated with both the treatment and the outcome, or with the outcome only, while avoiding the inclusion of covariates associated with treatment only. As such, any covariate found to be significantly associated with the outcome in preliminary univariate Cox proportional hazard regression models at an alpha <0.1 were included in the propensity score model. Average Treatment effect on Treated (ATT) weights were estimated based on the propensity score and ATT weighted Cox proportional hazards models were used to determine the association of treatment choice with OS. To account for residual confounding not captured by the propensity score all variables were considered for inclusion in the ATT weighted multivariable Cox model, with those having an alpha <0.1 included in the final model.

Results

In total, 278 patients with HER2+ mBC received T-DM1 and 34 lapatinib plus chemotherapy. The majority of patients in the lapatinib plus chemotherapy arm received a capecitabine-based chemotherapy regimen (91.18%) with the remainder receiving vinorelbine or eribulin.

Table 1. Patient demographic and clinical characteristics by treatment group.

Variable name	Category/measure	Trastuzumab emtansine	Lapatinib plus chemo	p-value
		n (%)	n (%)	
Age	Median (IQR†)	60 (53–69)	60 (54–66)	0.64
Gender	Female	277 (99.64)	34 (100)	1
	Male	1 (0.36)	0 (0)	
Ethnicity	White	170 (61.15)	21 (61.76)	0.59
	Asian	5 (1.8)	2 (5.88)	
	Black or African American	50 (17.99)	6 (17.65)	
	Hispanic or Latino	3 (1.08)	0 (0)	
	Missing/others	50 (17.99)	5 (14.71)	
ECOG‡ performance score	0	63 (22.66)	5 (14.71)	0.73
	1	89 (32.01)	11 (32.35)	
	2	50 (17.99)	6 (17.65)	
	3	14 (5.04)	1 (2.94)	
	4	2 (0.72)	0 (0)	
	Missing	60 (21.58)	11 (32.35)	
Hormone receptor status	ER+§ or PR+¶	161 (57.91)	18 (52.94)	0.63
	ER- and PR-	116 (41.73)	16 (47.06)	
	Unknown	1 (0.36)	0 (0)	
Disease stage	I	24 (8.63)	2 (5.88)	0.79
	II	64 (23.02)	6 (17.65)	
	III	57 (20.5)	6 (17.65)	
	IV	117 (42.09)	17 (50)	
	Not documented	16 (5.76)	3 (8.82)	
Site of disease involvement	Visceral	203 (73.02)	31 (91.18)	0.02
	Nonvisceral	75 (26.98)	3 (8.82)	
Metastatic sites	Brain/CNS#	62 (22.3)	20 (58.82)	<0.0001
	Bone	157 (56.47)	21 (61.76)	0.69
	Liver	113 (40.65)	12 (35.29)	0.68
	Lung	117 (42.09)	17 (50)	0.49
Number of metastatic sites	1	82 (29.5)	4 (11.76)	0.07
	2	76 (27.34)	10 (29.41)	
	≥3	120 (43.17)	20 (58.82)	
	Median (IQR)	2 (1–3)	3 (2–4)	
First-line treatment for mBC††	Monotherapy: trastuzumab	14 (5.04)	1 (2.94)	0.42
	Dual therapy: trastuzumab + taxane	17 (6.12)	2 (5.88)	
	Dual therapy: trastuzumab + targeted	15 (5.4)	5 (14.71)	
	Dual therapy: trastuzumab + other	18 (6.47)	4 (11.76)	
	Triple therapy: trastuzumab + taxane + targeted	161 (57.91)	16 (47.06)	
	Triple therapy: trastuzumab + taxane + other	10 (3.6)	0 (0)	
	Triple therapy: trastuzumab + targeted + other	12 (4.32)	1 (2.94)	
	Triple therapy: trastuzumab + other(s)	1 (0.36)	0 (0)	
	>Triple therapy	30 (10.79)	5 (14.71)	
Time between first- and second-line treatment initiation (years)	Median (IQR)	0.85 (0.44–1.49)	1.05 (0.55–1.5)	0.96
Treatment initiation year	2011	0 (0)	1 (2.94)	<0.0001

†IQR.
‡Eastern Cooperative Oncology Group.
§Estrogen receptor.
¶Progesterone receptor.
#CNS.
††Metastatic breast cancer.
‡‡Not Applicable.
CNS: Central nervous system; IQR: Interquartile range.

Table 1. Patient demographic and clinical characteristics by treatment group (cont.).

Variable name	Category/measure	Trastuzumab emtansine	Lapatinib plus chemo	p-value
		n (%)	n (%)	
	2012	0 (0)	3 (8.82)	
	2013	10 (3.6)	2 (5.88)	
	2014	34 (12.23)	4 (11.76)	
	2015	40 (14.39)	1 (2.94)	
	2016	31 (11.15)	2 (5.88)	
	2017	42 (15.11)	8 (23.53)	
	2018	41 (14.75)	6 (17.65)	
	2019	67 (24.10)	6 (17.65)	
	2020	13 (4.68)	1 (2.94)	
Comorbidities from the Charlson comorbidity index	Myocardial infarction	0 (0)	0 (0)	N/A‡‡
	Congestive heart failure	9 (3.24)	1 (2.94)	1
	Peripheral vascular disease	2 (0.72)	0 (0)	1
	Cerebrovascular disease	1 (0.36)	1 (2.94)	0.2
	Dementia	0 (0)	0 (0)	N/A
	Chronic pulmonary disease	9 (3.24)	1 (2.94)	1
	Rheumatic disease	3 (1.08)	0 (0)	1
	Peptic ulcer disease	1 (0.36)	0 (0)	1
	Diabetes without chronic complication	16 (5.76)	2 (5.88)	1
	Diabetes with chronic complication	0 (0)	0 (0)	N/A
	Hemiplegia or paraplegia	0 (0)	0 (0)	N/A
	Renal disease	9 (3.24)	1 (2.94)	1
	AIDS/HIV	0 (0)	0 (0)	N/A
	Mild liver disease	4 (1.44)	2 (5.88)	0.13
	Moderate or severe liver disease	0 (0)	0 (0)	N/A
Any comorbidity from the Charlson comorbidity index	Present	44 (15.83)	4 (11.76)	0.8
	Not present	234 (84.17)	30 (88.24)	
Payer category	Commercial health plan	124 (44.6)	19 (55.88)	0.77
	Medicare	29 (10.43)	3 (8.82)	
	Medicaid	8 (2.88)	1 (2.94)	
	Other Government program	4 (1.44)	1 (2.94)	
	Patient assistance program	8 (2.88)	1 (2.94)	
	Other payer – type unknown	34 (12.23)	2 (5.88)	
	Self pay	1 (0.36)	0 (0)	
	Missing	70 (25.18)	7 (20.59)	
Clinical practice	Academic	14 (5.04)	2 (5.88)	0.69
	Community	264 (94.96)	32 (94.12)	

†IQR.
‡Eastern Cooperative Oncology Group.
§Estrogen receptor.
¶Progesterone receptor.
#CNS.
††Metastatic breast cancer.
‡‡Not Applicable.
CNS: Central nervous system; IQR: Interquartile range.

Patient characteristics are described in Table 1. In terms of their first-line treatment of mBC, the use of triple therapy with a taxane and targeted therapy alongside trastuzumab was more common in patients treated with T-DM1 (57.9%) than lapatinib plus chemotherapy (47.1%) and the use of trastuzumab monotherapy was more common in T-DM1 patients (5.0%) than lapatinib plus chemotherapy patients (2.9%). Despite this, the median

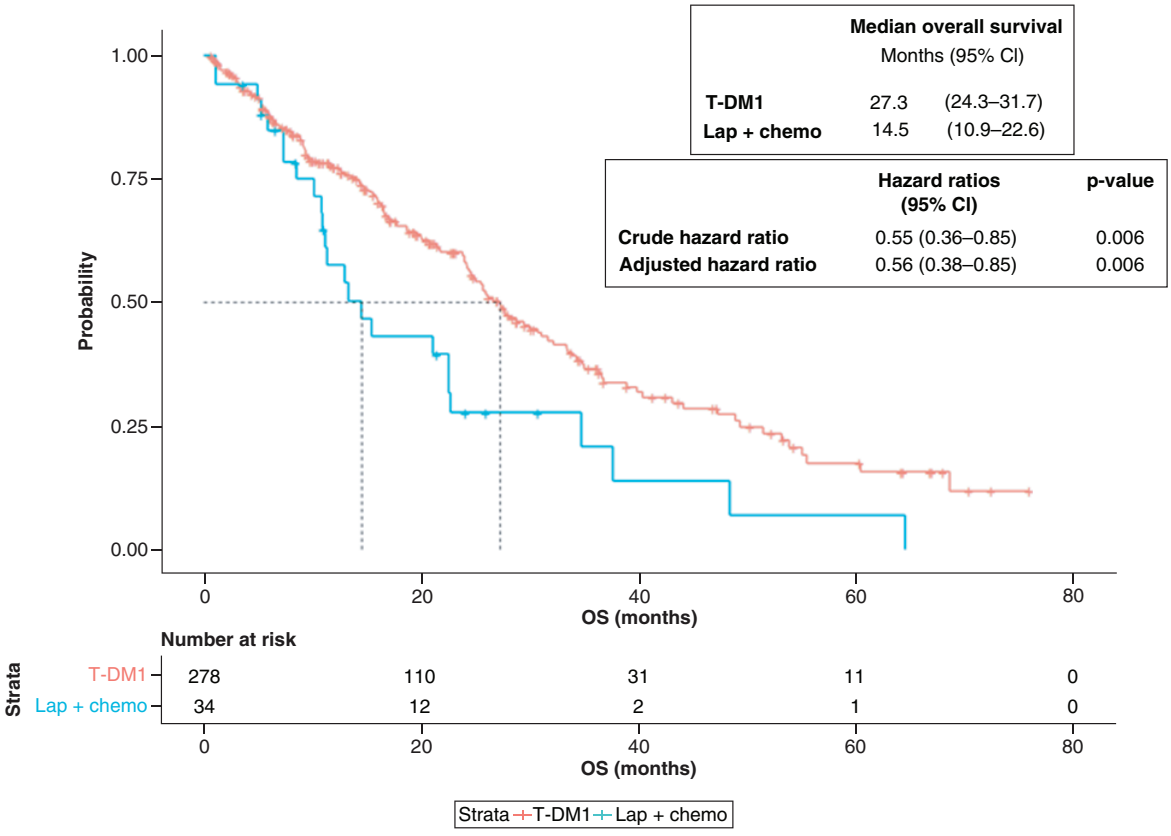

Figure 1. Kaplan–Meier estimates of overall survival for HER2+ metastatic breast cancer patients in Flatiron Health previously treated with trastuzumab. Survival function estimates for patients receiving T-DM1 and patients receiving lapatinib plus chemotherapy are shown in red and blue, respectively.
OS: Overall survival; T-DM1: Trastuzumab emtansine.

time between initiation of 1L treatment and initiation of 2L treatment was greater for patients receiving lapatinib plus chemotherapy (1.05 years) than those receiving T-DM1 (0.85 years). Patients treated with lapatinib plus chemotherapy had a greater amount of visceral disease (91.2 vs 73.0% more brain metastases [58.8 vs 22.3%] and a greater number of metastatic sites (median 3 sites vs 2 sites) than T-DM1 patients.

Median follow-up was 28.4 months in the T-DM1 patients and 30.8 months in the lapatinib plus chemotherapy patients. The crude hazard of death was lower in the T-DM1 patients compared with the lapatinib plus chemotherapy patients (HR: 0.55; 95% CI: 0.36–0.85).

The following variables were found to be significantly associated with survival in univariate models and included in the logistic regression model used to estimate the propensity score: age at treatment initiation, metastatic sites (bone, brain/CNS), number of metastatic sites and time between first- and second-line treatment initiation (data not shown). Two patients were dropped from the study population in estimating the propensity score in order to improve population overlap leaving 310 patients for the adjusted analyses. Age and time between first- and second-line treatment had standardized mean differences after weighting of -0.183 and 0.274, respectively; all other variables had standardized mean differences <0.1. The final ATT weighted multivariable Cox model additionally adjusted for ECOG performance status at treatment initiation, metastatic site(s), number of metastatic sites, first-line treatment, insurance status and presence of a Charlson comorbidity. Results from this model were similar to the crude results, with the crude hazard of death lower in the T-DM1 patients compared with the lapatinib plus chemotherapy patients (HR: 0.56; 95% CI: 0.38–0.85; Table 2 & Figure 1).

Discussion

Overall survival in this real-world cohort of HER2+ mBC patients was significantly longer in patients treated with T-DM1 than in patients treated with lapatinib plus chemotherapy.

Table 2. Multivariable Cox proportional hazard model results (n = 310).

		Hazard ratio (95% CI[†])
Treatment	Lapatinib plus chemotherapy	Ref[‡]
	Trastuzumab emtansine	0.56 (0.38–0.85)
ECOG performance score	≤2	Ref
	>2	1.44 (0.50–4.11)
	Missing	2.06 (1.32–3.21)
Metastatic site	Not present	Ref
	Brain/CNS	2.65 (1.50–4.66)
	Bone	0.42 (0.27–0.66)
	Liver	1.01 (0.65–1.55)
	Lung	1.19 (0.77–1.82)
Number of metastatic sites	1	Ref
	2	2.46 (1.29–4.69)
	≥3	4.32 (2.01–9.31)
First-line treatment for mBC	Triple therapy: trastuzumab + targeted + other	Ref
	>Triple therapy	6.22 (0.97–39.72)
	Dual therapy: trastuzumab + other	5.27 (0.94–29.40)
	Dual therapy: trastuzumab + targeted	3.23 (0.59–17.80)
	Dual therapy: trastuzumab + taxane	7.15 (1.26–40.50)
	Monotherapy: trastuzumab	2.17 (0.35–13.36)
	Trastuzumab + taxane + targeted/other	3.31 (0.64–17.26)
Any comorbidity from the Charlson comorbidity index	Not present	Ref
	Present	2.08 (1.19–3.63)
Payer category	Missing	Ref
	Commercial health plan	1.89 (1.11–3.23)
	Medicaid	0.31 (0.09–1.02)
	Medicare	1.75 (0.78–3.93)
	Other Government program	0.23 (0.06–0.87)
	Other payer – type unknown	1.41 (0.74–2.68)
	Patient assistance program	2.29 (0.88–6.00)

[†]CI.
[‡]Reference.
CNS: Central nervous system; ECOG: Eastern Cooperative Oncology Group; mBC: Metastatic breast cancer.

Direct comparison of the results presented here with those of the EMILIA trial are complicated by differences in the populations captured in each study. Individuals in the current FH study population were on an average slightly older than those in the EMILIA trial and the current study population included individuals with an ECOG greater than one where the EMILIA population did not. Another difference between the studies is that all patients in the EMILIA trial received a capecitabine-based chemotherapy regimen alongside lapatinib while only 91% of patients in the equivalent arm of our study received a capecitabine-based chemotherapy regimen. Despite these differences, our findings suggest a similar magnitude of relative benefit in those treated with T-DM1 to that reported for the EMILIA trial [1]. Notably, as the population captured in this study is broader than that in the EMILIA trial, the results go beyond those of the trial, supporting the comparative effectiveness of T-DM1 in a broader real-world population receiving a set of treatments reflective of those received in routine clinical practice.

Previous real-world studies of T-DM1 have reported absolute estimates of effectiveness in HER2+ mBC patients treated with T-DM1 and have provided comparisons of T-DM1 effectiveness between T-DM1 patients treated with different prior treatment regimens or with differing severity of disease [4–9], our study provides estimates of absolute effectiveness of T-DM1 in a larger cohort of second-line mBC patients than observed in any of these studies. Further, while these studies focused on absolute effectiveness, to our knowledge ours is the first to report on the real-world effectiveness of T-DM1 in second-line mBC relative to an alternative treatment option in this setting.

Limitations of the FH database and Electronic Health Records in general are well documented and include incomplete information on some variables such as comorbidities, metastases, performance status, date of death and adjuvant/neoadjuvant treatments [3,10]. As expected for a real-world study where treatments are not given at random, differences were observed in patient characteristics and prognostic factors between the two treatment groups. While we did our best to adjust for these in multivariable analyses, as with any nonrandomized study, the possibility of residual confounding must be considered in the interpretation of our results. Only statistical associations rather than causal relationships can therefore be concluded. Our analysis is also limited by the relatively small size of the lapatinib plus chemotherapy arm and the short median follow-up of the cohort. Our analysis should therefore be viewed as exploratory and not definitive, and further work is needed to confirm our findings. Despite these limitations, the results suggest the benefit of T-DM1 demonstrated in clinical trials is being realized in real-world populations, including populations not captured in these trials.

Conclusion

Real-world data supports the effectiveness of T-DM1 in the second-line treatment of HER2+ mBC patients previously treated with trastuzumab.

Summary points

- Positive results from the EMILIA trial have led to the widespread use of trastuzumab emtansine (T-DM1) in HER2+ metastatic breast cancer (mBC).
- Despite this, few studies have explored the realization of these trial results in real-world populations.
- The Flatiron Health database was used to identify a cohort of HER2+ mBC patients who received first-line trastuzumab treatment and T-DM1 or lapatinib plus chemotherapy as second-line treatment.
- Overall survival was compared using Cox regression models adjusting for differences in patient characteristics.
- 278 patients with HER2+ mBC received second-line T-DM1 and 34 lapatinib plus chemotherapy.
- Overall survival was longer in patients treated with T-DM1 than those treated with lapatinib plus chemotherapy (adjusted hazard ratio: 0.56; 95% CI: 0.38–0.85).
- Real-world data supports the effectiveness of T-DM1 in the second-line treatment of HER2+ mBC patients.

Author contributions

SV Ramagopalan, J Ray and C Sammon were responsible for study conception and design; SV Ramagopalan, R Pisoni, A Zenin, J Ray, LS Rathore and C Sammon were responsible for data analysis, and drafting and revision of the manuscript.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors confirm that all the research meets the ethical guidelines, including adherence to the legal requirements of the study country.

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