Original Article

Patient-Reported Outcomes From EMILIA, a Randomized Phase 3 Study of Trastuzumab Emtansine (T-DM1) Versus Capecitabine and Lapatinib in Human Epidermal Growth Factor Receptor 2–Positive Locally Advanced or Metastatic Breast Cancer

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BACKGROUND: This report describes the results of an analysis of patient-reported outcomes from EMILIA (TDM4370g/BO21977), a randomized phase 3 study of the antibody–drug conjugate trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in human epidermal growth factor receptor 2 (HER2)–positive locally advanced or metastatic breast cancer. **METHODS:** A secondary endpoint of the EMILIA study was time to symptom worsening (time from randomization to the first documentation of a ≥5-point decrease from baseline) as measured by the Trial Outcome Index Physical/Functional/Breast (TOI-PFB) subset of the Functional Assessment of Cancer Therapy–Breast questionnaire. Predefined exploratory patient-reported outcome endpoints included proportion of patients with a clinically significant improvement in symptoms (per TOI-PFB) and proportion of patients with diarrhea symptoms (per Diarrhea Assessment Scale). **RESULTS:** In the T-DM1 arm, 450 of 495 patients had a baseline and ≥1 postbaseline TOI-PFB score versus 445 of 496 patients in the capecitabine-plus-lapatinib arm. Time to symptom worsening was delayed in the T-DM1 arm versus the capecitabine-plus-lapatinib arm (7.1 months versus 4.6 months, respectively; hazard ratio = 0.796; $P = .0121$). In the T-DM1 arm, 55.3% of patients developed clinically significant improvement in symptoms from baseline versus 49.4% in the capecitabine-plus-lapatinib arm ($P = .0842$). Although similar at baseline, the number of patients reporting diarrhea symptoms increased 1.5- to 2-fold during treatment with capecitabine and lapatinib but remained near baseline levels in the T-DM1 arm. **CONCLUSIONS:** Together with the EMILIA primary data, these results support the concept that T-DM1 has greater efficacy and tolerability than capecitabine plus lapatinib, which may translate into improvements in health-related quality of life. ***Cancer*** **2014;120:642–51.** *© 2013 American Cancer Society.*

KEYWORDS: ado-trastuzumab emtansine, T-DM1, HER2-positive, quality of life, breast cancer, antibody–drug conjugate.

INTRODUCTION

Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate (ADC) comprising the humanized monoclonal antibody trastuzumab, a unique stable linker, and the highly potent cytotoxic agent DM1. In preclinical studies, it has been shown that T-DM1 delivers DM1 directly to human epidermal growth factor receptor 2 (HER2)–expressing tumor cells, where it is released intracellularly and causes apoptosis.[1] Similar to trastuzumab, T-DM1 inhibits cell signaling through the phosphatidylinositol 3-kinase/AKT pathway, inhibits HER2 shedding, and induces antibody-dependent cellular cytotoxicity.[2,3]

Results were recently reported from the randomized phase 3 EMILIA study (TDM4370g/BO21977; ClinicalTrials.gov identifier NCT00829166) comparing T-DM1 with capecitabine plus lapatinib for patients with HER2-positive, locally advanced (LABC) or metastatic breast cancer (MBC) previously treated with a taxane and trastuzumab. Patients who were treated with T-DM1 had significantly longer progression-free survival (PFS; 9.6 months versus 6.4 months; hazard ratio [HR] = 0.65; $P < .001$) and overall survival (OS; 30.9 months versus 25.1 months; HR = 0.68;

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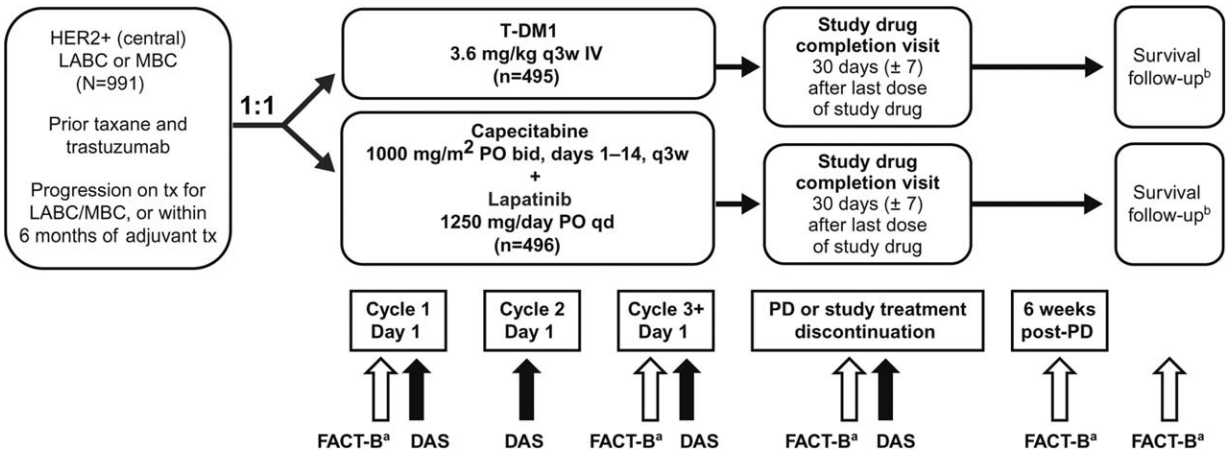

Figure 1. The EMILIA study design and PRO assessment schedule is illustrated. FACT-B assessments were performed on day 1 of cycle 1 and every second cycle thereafter until 6 weeks after PD and DAS assessments were performed on day 1 of each cycle during the treatment phase. Abbreviations: bid, twice a day; DAS, Diarrhea Assessment Scale; FACT-B, Functional Assessment of Cancer Therapy–Breast; HER2+, human epidermal growth factor receptor 2–positive; IV, intravenous; LABC, locally advanced breast cancer; MBC, metastatic breast cancer; PD, disease progression; PO, orally; PRO, patient-reported outcomes; q3w, once every 3 weeks; qd, once a day; T-DM1, trastuzumab emtansine; tx, treatment. [a]Female patients only. [b]Approximately every 3 months starting from the study drug completion visit until death, loss to follow-up, withdrawal of consent, or study discontinuation.

$P < .001$), as well as fewer adverse events of grade 3 or greater, compared with those treated with capecitabine and lapatinib: 41% (95% confidence interval [CI] = 37%-45%) versus 57% (95% CI = 53%-61%).[4] Based on these results, the US Food and Drug Administration recently approved T-DM1 for the treatment of HER2-positive MBC previously treated with trastuzumab and taxane chemotherapy.

Despite the demonstrated activity and favorable safety profile associated with T-DM1, it is important to ensure that improved clinical outcomes do not come at the expense of a patient's symptom burden. Patient-reported outcomes (PROs) provide a means of evaluating the subjective effect treatments have on patients and their quality of life (QOL).[5] It is also important to understand the profile of adverse events from the patient's perspective. Basch et al demonstrated that the incidence and severity of adverse events, as reported by investigators in clinical trials, can differ from reports of adverse events provided by patients.[6,7] This difference can be particularly evident in cases of subjective adverse events, such as fatigue.

PRO data have been reported from 2 previous phase 2 studies of single-agent T-DM1 administered once every 3 weeks (q3w). In TDM4374g, an open-label study of T-DM1 in patients with pretreated HER2-positive MBC (median of 7 prior agents for metastatic disease), PRO data suggested that T-DM1 is well tolerated and that treatment with T-DM1 does not increase symptom burden.[8] In addition, in the randomized phase 2 study TDM4450g, the favorable safety profile associated with T-DM1 appeared to translate into superior overall QOL versus first-line treatment with trastuzumab and docetaxel.[9] To obtain a better understanding of PROs with T-DM1, a secondary endpoint of the pivotal phase 3 EMILIA study was patient-reported time to symptom worsening. Here, we report the results of an EMILIA QOL analysis to evaluate the impact of T-DM1 and capecitabine plus lapatinib on PROs.

MATERIALS AND METHODS

Study Design

In the EMILIA study, patients with HER2-positive, unresectable LABC or MBC, who were previously treated with trastuzumab and a taxane, were randomized in a 1:1 ratio to T-DM1 (3.6 mg/kg intravenously q3w) or capecitabine (1000 mg/m^2 orally [po] twice a day, on days 1 through 14 of a q3w cycle) plus lapatinib (1250 mg po daily) until disease progression (PD) or unmanageable toxicity (Fig. 1). The study design and patient characteristics have been reported.[4] Patients provided written informed consent; the study was approved by the relevant institutional review board and/or independent ethics committee at each study site.

PRO Assessments

Functional Assessment of Cancer Therapy–Breast (FACT-B) is a 37-item questionnaire with a 7-day recall period composed of 5 subscales that measure physical,

functional, social, and emotional well-being, as well as breast cancer–related symptoms. Female patients were asked to complete the FACT-B on day 1 of cycle 1 and every second cycle thereafter until 6 weeks after PD (or at the time of tumor assessment for patients who discontinued study treatment for reasons other than PD). The FACT-B was also given at the study drug completion visit and every 3 months thereafter at survival follow-up visits (Fig. 1).

The FACT-B Trial Outcome Index Physical/Functional/Breast (TOI-PFB) is a 23-item subset of the FACT-B that can be used as a summary measure of physical and functional well-being in patients with breast cancer.[10] Scores range from 0 to 92 points; a higher score indicates a better QOL. A change of ≥ 5 points is considered clinically meaningful (ie, patients would have experienced clinically significant changes in health-related well-being).[10-12] On this basis, the primary PRO endpoint in EMILIA was the time to symptom worsening as measured by the FACT-B TOI-PFB, which was defined as the time from randomization to the first documentation of a decrease of ≥ 5 points from baseline.

Predefined exploratory PRO endpoints in EMILIA included 1) the proportion of patients with a clinically significant improvement in symptoms between the 2 treatment arms as measured by the FACT-B TOI-PFB and 2) the proportion of patients with diarrhea symptoms as measured by the Diarrhea Assessment Scale (DAS). A patient was considered to have a clinically significant improvement in TOI-PFB score if the patient had at least one 5-point postbaseline increase in TOI-PFB score compared with baseline. The DAS is a 4-item questionnaire designed to evaluate the frequency, urgency, consistency, and discomfort of diarrhea experienced by a patient on a 4-point scale[13,14] with a 7-day recall period. The DAS was administered on day 1 of each cycle before the final analysis of PFS, after which the DAS was no longer administered. The incidence of each of the 4 diarrhea symptoms was calculated for both treatment arms at baseline and for each cycle in female patients with a baseline and ≥ 1 follow-up assessment.

Ad hoc exploratory (hypothesis-generating) PRO analyses included an evaluation of mean changes from baseline between treatment arms on the FACT-B physical well-being (PWB) subscale. The PWB subscale of the FACT-B contains 7 questions (scale 0 to 4) that measure physical symptoms related to adverse events. A difference of 5% of the scale range, or 0.25, is considered clinically meaningful, based on findings from published studies of minimally important differences in cancer scales.[12,15]

Statistical Analyses

For the primary PRO analysis, time to symptom worsening was assessed by Kaplan-Meier methods and a Cox model in female patients with baseline and ≥ 1 postbaseline TOI-PFB score, stratified by world region (United States, Western Europe, other); number of prior chemotherapeutic regimens for unresectable, locally advanced, or metastatic disease (0-1 versus > 1); and visceral versus nonvisceral disease. Two sensitivity analyses were performed for the primary analysis. In the first sensitivity analysis, symptom worsening that occurred after 1 or more missing assessments was backdated to the last nonmissing TOI-PFB assessment date plus 1 to assess the effect of missing assessments on the results. In the second sensitivity analysis, the date of symptom worsening was backdated by 6 weeks to assess the impact of the potential bias due to delayed reporting of symptom worsening. Log-rank P values were calculated, and the 95% CI for the median was computed using the method of Brookmeyer and Crowley.[16]

Descriptive statistics (mean, standard error, minimum, and maximum) were used to evaluate the change from baseline in FACT-B TOI-PFB scores for each visit by treatment arm. In addition, a mixed-effects repeated measure model[17] was used to evaluate the change from baseline in FACT-B TOI-PFB scores. Change from baseline in TOI-PFB score was the response variable; treatment, visit, and treatment-by-visit interaction terms were the fixed effects; baseline TOI-PFB score was the covariate; and within-subject correlation was modeled with a compound symmetry covariance structure. The treatment effects at week 12, 24, 36, and study drug termination visits were compared between the 2 treatment arms with the least-squares t tests in the mixed-effects model.

The proportion of patients with a clinically significant improvement in TOI-PFB score in each treatment arm was estimated with 95% CIs calculated by using the Blyth-Still-Casella method.[18,19] Treatment arms were compared, and a P value was computed using the stratified Mantel-Haenszel chi-squared test.[20] For the DAS, summary statistics (frequency and proportion) by collapsed categories were used. Differences in the proportion of patients with moderate to severe diarrhea between treatment arms and 95% CIs were calculated.

In an ad hoc exploratory analysis, a repeated measure mixed-effects model[17] was used to estimate least squares means of change from baseline PWB sub-item scores. Treatment, time, and treatment-by-time interaction were fixed effects; baseline score was a covariate; and within-subject correlation was modeled with a compound symmetry covariance structure.

The compliance rates of TOI-PFB reporting were summarized by each visit. The compliance rates were calculated as the ratio of the number of patients with nonmissing TOI scores divided by the number of patients expected to complete the FACT-B questionnaire as per the protocol.

RESULTS

Patient Characteristics

In total, 991 patients were randomized to the capecitabine-plus-lapatinib (n = 496) and the T-DM1 (n = 495) arms, respectively. Baseline demographics and disease characteristics were balanced between treatment arms.[4] A total of 895 of 986 female patients had a baseline and ≥ 1 postbaseline TOI-PFB score, comprising 445 of 496 patients in the capecitabine-plus-lapatinib arm and 450 of 495 patients in the T-DM1 arm.

Compliance With Completion of TOI-PFB Questionnaire

The completion rates of TOI-PFB were 93.8% and 89.3% at week 6 in the T-DM1 and capecitabine-plus-lapatinib arms, respectively. The completion rates for the T-DM1 arm were consistently higher than those reported in the capecitabine-plus-lapatinib arm at all time points except week 30. Thereafter, completion rates gradually declined to 71.4% and 70.0%, respectively, at week 48. Completion rates at the study drug completion visit were 80.2% in the T-DM1 arm and 70.9% in the capecitabine-plus-lapatinib arm. Completion rates were lower during the survival follow-up period (after study drug discontinuation) and declined gradually at each 3-month period: 50.3% and 48.0% for T-DM1 and capecitabine plus lapatinib, respectively, at month 3, to 22.6% and 12.9%, respectively, at month 12 (Table 1).

Primary Analysis: Time to Symptom Worsening

Of the 450 patients in the T-DM1 arm and 445 patients in the capecitabine-plus-lapatinib arm who were eligible for the analysis of time to symptom worsening, 246 patients (54.7%) and 257 patients (57.8%), respectively, had worsening of symptoms. Median time to symptom worsening, as measured by the FACT-B TOI-PFB, was longer in the T-DM1 arm compared with the capecitabine-plus-lapatinib arm (7.1 months versus 4.6 months; HR = 0.796, 95% CI = 0.667-0.951; P = .0121, based on the stratified analysis) (Fig. 2).[4] The results of an unstratified analysis were consistent with these findings (data not shown).

In addition, the results of 2 sensitivity analyses also demonstrated an increase in the median time to symptom worsening for patients who received T-DM1 compared with patients who received capecitabine plus lapatinib. The sensitivity analysis used to assess the impact of missing assessments resulted in a median time to symptom worsening of 6.0 months for the T-DM1 arm versus 4.3 months for the capecitabine-plus-lapatinib arm (HR = 0.788, 95% CI = 0.660-0.941; P = .0089; stratified analysis). The analysis evaluating

TABLE 1. Compliance With Completion of the FACT-B TOI-PFB Questionnaire From Randomized Female Patients With Baseline and ≥1 Postbaseline Valid Score

	Patients With Nonmissing TOI-PFB Score Out of Patients Expected per Protocol	
	Capecitabine + Lapatinib (n = 445), n/N (%)	Trastuzumab Emtansine (n = 450), n/N (%)
Before Disease Progression		
Baseline	445/445 (100)	450/450 (100)
Week 6	375/420 (89.3)	405/432 (93.8)
Week 12	318/377 (84.4)	346/388 (89.2)
Week 18	221/304 (72.7)	289/344 (84.0)
Week 24	158/216 (73.1)	225/278 (80.9)
Week 30	99/170 (58.2)	116/232 (50.0)
Week 36	96/138 (69.6)	142/186 (76.3)
Week 42	67/110 (60.9)	98/161 (60.9)
Week 48	56/80 (70.0)	90/126 (71.4)
Study Drug Completion Visit	210/296 (70.9)	203/253 (80.2)
Survival Follow-up Period		
Month 3	96/200 (48.0)	88/175 (50.3)
Month 6	51/158 (32.3)	54/134 (40.3)
Month 9	31/129 (24.0)	35/105 (33.3)
Month 12	15/116 (12.9)	19/84 (22.6)

Abbreviations: FACT-B, Functional Assessment of Cancer Therapy–Breast; TOI-PFB, Trial Outcome Index Physical/Functional/Breast.

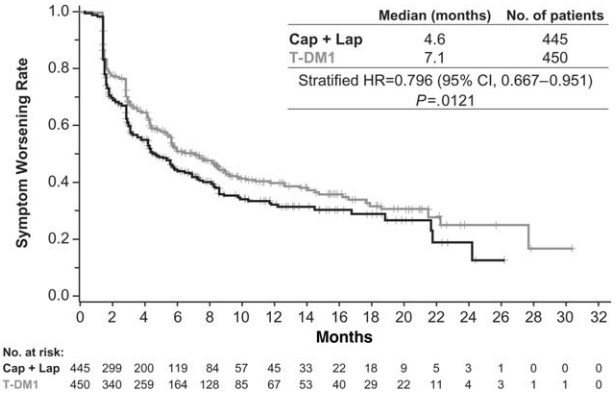

Figure 2. Time to symptom worsening, based on randomized female patients with baseline and ≥1 postbaseline valid score. Abbreviations: Cap, capecitabine; CI, confidence interval; HR, hazard ratio; Lap, lapatinib; T-DM1, trastuzumab emtansine.

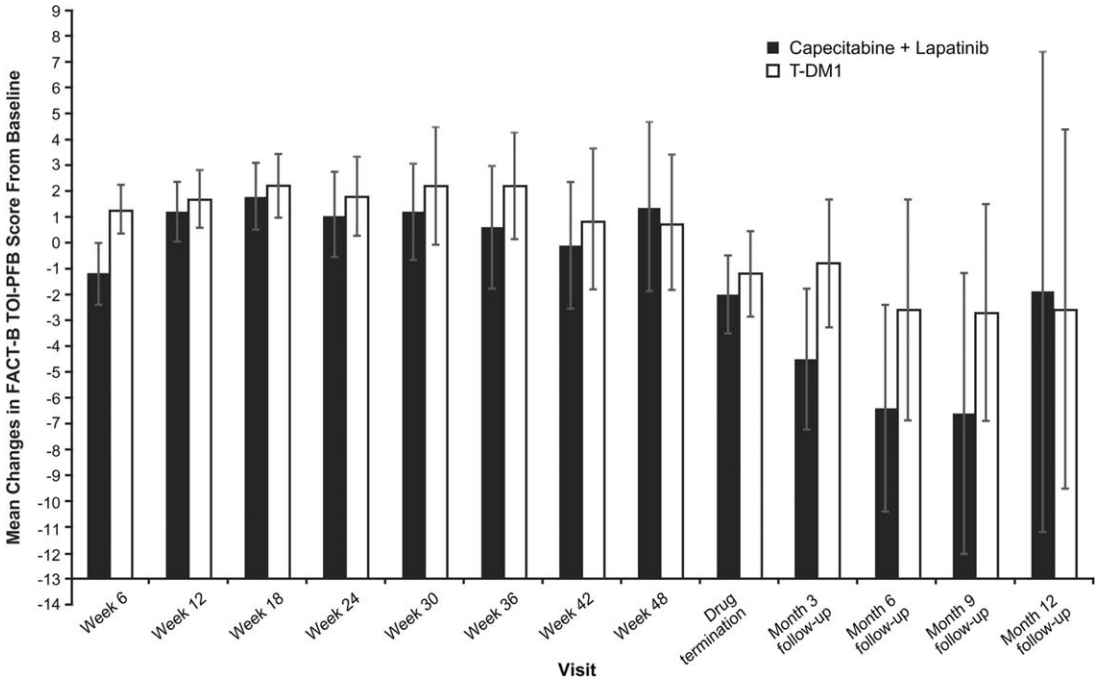

Figure 3. Mean changes in FACT-B TOI-PFB scores of T-DM1 versus capecitabine plus lapatinib. Error bars indicate 95% confidence intervals. Abbreviations: FACT-B, Functional Assessment of Cancer Therapy–Breast; T-DM1, trastuzumab emtansine; TOI-PFB, Trial Outcome Index Physical/Functional/Breast.

the impact of potential bias caused by delayed reporting of symptom worsening resulted in 6.6 months versus 4.2 months, respectively (HR = 0.820, 95% CI = 0.686-0.979; $P = .0286$; stratified analysis). These results are consistent with and support those observed in the primary analysis.

Predefined Exploratory Analyses

A descriptive summary of mean changes in FACT-B TOI-PFB scores from baseline per visit is shown in Figure 3. In both arms, the average postbaseline TOI-PFB scores were slightly higher than baseline scores for visits before study drug termination but lower for visits after study drug termination. Patients in the T-DM1 arm reported more favorable TOI-PFB score changes compared with those in the capecitabine-plus-lapatinib arm for all but 2 visits (week 48 on study drug and month 12 after study drug termination). The repeated measure mixed-effects model analysis showed a mean difference in TOI-PFB of 1.30 points (95% CI = −0.15 to 2.74; $P = .0783$) at week 12; 0.86 points (95% CI = −0.83 to 2.55; $P = .3195$) at week 24; 1.28 points (95% CI = −0.67 to 3.15; $P = .2023$) at week 36; and 1.07 points (95% CI = −0.59 to 2.73; $P = .2068$) at the drug termination visit, which all numerically favored T-DM1. In the mixed-effects model, the main effect of time and interaction effect of time by treatment were both statistically significant ($P < .0001$ and $P = .0302$, respectively).

In the T-DM1 arm, 55.3% of patients (249 of 450; 95% CI = 50.7%-60.0%) had a clinically significant improvement in symptoms from baseline compared with 49.4% of patients in the capecitabine-plus-lapatinib arm (220 of 445; 95% CI = 44.7%-54.2%; $P = .0842$, based on a stratified analysis).

Although similar at baseline, the number of patients reporting diarrhea symptoms increased 1.5- to 2-fold during treatment in the capecitabine-plus-lapatinib arm, whereas the number reporting diarrhea symptoms remained near baseline levels in the T-DM1 arm (Fig. 4). At cycle 2, more patients in the capecitabine-plus-lapatinib arm versus the T-DM1 arm had more than 1 stool per day (60.5% versus 31.7%), had unformed stools (75.1% versus 39.5%), developed urgency (60.2% versus 27.5%), and had abdominal discomfort (51.0% versus 27.3%).

Ad Hoc Exploratory Analysis

In the FACT-B PWB subscale, there was a clinically meaningful improvement in the item "bothered by side effects" for patients in the T-DM1 arm compared with

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